

5.11 TAFAMIDIS, Capsule 61 mg, Vyndamax[®], Pfizer Australia Pty Ltd.

1 Purpose of submission

- 1.1 The submission requested an Authority Required (written) listing for tafamidis 61 mg capsules, for the treatment of patients with transthyretin amyloid cardiomyopathy (ATTR-CM) with evidence of cardiac involvement by echocardiography and with a history of heart failure.
- 1.2 Listing was requested on the basis of a cost effectiveness analysis versus standard management of ATTR-CM (best supportive care). The PBAC has not previously considered tafamidis.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Patients with transthyretin amyloid cardiomyopathy with evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness \geq 12 mm.
Intervention	Tafamidis 61 mg capsule, once daily.
Comparator	Standard heart failure management (e.g. diuretics and anti-arrhythmic medicines).
Outcomes	Mortality, cardiovascular-related hospitalisations, functional measures (6 Minute Walk Test), quality of life (KCCQ-OS score, EQ-5D-3L).
Clinical claim	Tafamidis has superior efficacy and non-inferior safety to standard heart failure management.

Source: Table 1.1.1, p.24 of the submission.

Abbreviations: EQ-5D-3L, EuroQoL 5 dimension 3 level questionnaire; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire - overall score.

2 Background

Registration status

- 2.1 Tafamidis 61 mg and tafamidis meglumine 20 mg were registered by the TGA for “the treatment of adult patients with wild-type or hereditary transthyretin amyloid cardiomyopathy (ATTR-CM)” on 16 March 2020.
- 2.2 Tafamidis 61 mg is considered bioequivalent to tafamidis meglumine 80 mg formulation (four 20 mg capsules), used in the key clinical trial (TGA Clinical Evaluation Report: Round 2, p.58).
- 2.3 The Advisory Committee on Medicines (ACM) advised that ideally, tafamidis would be administered to patients prior to reaching New York Heart Association (NYHA) Class III ATTR-CM, as the major efficacy benefits of tafamidis were demonstrated in NYHA Classes I and II. However, the ACM considered the efficacy of tafamidis in NYHA Class III to be acceptable (Resolution of the Advisory Committee on Medicines, Meeting 19).

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

3.1 The restriction requested in the submission is outlined below. The PBAC’s suggested additions are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
TAFAMIDIS 61 mg capsules (30)	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Vyndamax® Pfizer Australia Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – non-immediate/delayed assessment by Services Australia (In-writing only via mail/postal service or electronic upload to Hobart)
Condition: Transthyretin amyloid cardiomyopathy (ATTR-CM) due to wild type or variant transthyretin
Indication: Transthyretin amyloid cardiomyopathy
Treatment Phase: Initial treatment
Clinical criteria: <i>The condition must be wild type transthyretin amyloidosis; or</i> <i>The condition must be variant transthyretin type amyloidosis</i>
Clinical criteria: Patient must have evidence or has a history of heart failure
AND
Patient must have New York Heart Association Class I to III heart failure
AND
Patient must have evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness \geq of at least 12 mm
AND
The condition must have the presence of transthyretin precursor protein in cardiac tissue as identified by one of the following: (i) <i>histological confirmation with either immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry;</i> <i>or</i> (ii) <i>Grade 2/3 bone scintigraphy with technetium-labelled radioactive tracer in addition to negative results for monoclonal protein on each of the following three tests: serum immunofixation and electrophoresis; urine immunofixation and electrophoresis; and serum free light chains.</i>
AND
Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 mL/minute/1.73m ²
Treatment criteria: Must be treated by a <i>specialist cardiologist</i> ; or Must be treated by a consultant physician with experience in the management of amyloid disorders
Prescribing Instructions: Evidence or history of heart failure must comprise one of the following: (i) <i>History of one or more hospitalisations for heart failure,</i> (ii) <i>Clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement</i>
Administrative Advice: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed Transthyretin Amyloid Cardiomyopathy (ATTR-CM) PBS Authority Application - Supporting Information Form <i>which seeks details of the following: (to be finalised)</i>
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services <i>Services Australia</i> on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).
Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au <i>Services Australia website at www.servicesaustralia.gov.au</i>

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Applications for authority to prescribe should be forwarded to: submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos

Or mailed to:
 Services Australia
 Department of Human Services
 Complex Drugs
 Reply Paid 9826
 HOBART TAS 7001

Patient has documented ATTR-CM (variant or wild type) as demonstrated by either:

- Negative results for monoclonal protein on all three tests:
 - serum immunofixation and electrophoresis AND
 - urine immunofixation and electrophoresis, AND
 - serum free light chains;
 - AND
 - Transthyretin precursor protein identified by:
 - Grade 2 or 3 on bone scintigraphy with technetium-labelled radioactive tracer e.g., 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC-PYP [pyrophosphate] or 99mTC-HDP [99mTC-labelled hydroxymethylene diphosphate (HMDP)]; OR
 - Histological confirmation with immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry;
- OR
- Negative results for monoclonal protein on all three tests:
 - serum immunofixation and electrophoresis AND
 - urine immunofixation and electrophoresis, AND
 - serum free light chains;
 - AND
 - Transthyretin precursor protein identified by:
 - Grade 1 on bone scintigraphy with technetium-labelled radioactive tracer e.g., 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC-PYP [pyrophosphate] or 99mTC-HDP [99mTC-labelled hydroxymethylene diphosphate (HMDP)]; AND
 - Histological confirmation with immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry;
- OR
- Positive result for monoclonal protein on one of the following three tests:
 - serum immunofixation and electrophoresis OR
 - urine immunofixation and electrophoresis OR
 - serum free light chains;
 - AND
 - Transthyretin precursor protein identified by:
 - Grade 1, 2 or 3 on bone scintigraphy with technetium-labelled radioactive tracer e.g., 99mTC-DPD [99mTC-3,3-diphosphono-1,2-propano-dicarboxylic acid], 99mTC-PYP [pyrophosphate] or 99mTC-HDP [99mTC-labelled hydroxymethylene diphosphate (HMDP)]; AND
 - Histological confirmation with immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry;

Tafamidis: continuing treatment Restriction Summary [new] / Treatment of Concept [new]

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type / Method: <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online)
Condition: Transthyretin amyloid cardiomyopathy (ATTR-CM) due to wild type or variant transthyretin
Indication: Transthyretin amyloid cardiomyopathy
Treatment Phase: Continuing treatment
Clinical criteria:
Patient must have previously received prior PBS-subsidised treatment with this drug for this condition
AND
Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 ml/minute/1.73m ²
AND:

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Patient must have New York Heart Association Class I to III heart failure
Treatment criteria:
Must be treated by a specialist cardiologist; or
Must be treated by a consultant physician with experience in the management of amyloid disorders
Must be treated in consultation with a specialist cardiologist
Prescribing Instructions:
The treatment must be ceased if any of the following occur:
(i) Patient progresses to New York Heart Association Class IV heart failure, or
(ii) Patient receives a heart / liver transplant, or
(iii) Patient receives an implanted cardiac ventricular assist device
Administrative Advice:
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to the Department of Human Services on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Department of Human Services website at www.humanservices.gov.au
Applications for authority to prescribe should be forwarded to: Department of Human Services Complex Drugs Reply Paid 9826 HOBART TAS 7004

- 3.2 The submission proposed a special pricing arrangement with a rebate of [REDACTED] % on the published price (effective price of \$ [REDACTED] DPMQ).
- 3.3 The proposed listing is for the tafamidis 61 mg free acid formulation which is considered to be bioequivalent to tafamidis meglumine 80 mg formulation that was used in the key trial. The sponsor has not requested PBS listing of the tafamidis meglumine 20 mg formulation.
- 3.4 The TGA Delegate’s Overview noted that the sponsor only proposed registration of the higher dose regimen (80 mg tafamidis meglumine or 61 mg tafamidis free acid daily), and that ‘most efficacy variables showed a similar benefit between 20 mg and 80 mg daily dosing of tafamidis meglumine however NT-proBNP results suggested a better profile with 80 mg’. The Advisory Committee on Medicines (ACM) resolution ‘noted that uncertainty exists regarding the optimal dosing for tafamidis. While there is no significant difference in efficacy between the two doses, the 80 mg dose outcomes appear to be slightly more favourable compared to the 20 mg dose, so the ACM indicated a preference for the 80 mg dose’. The Product Information states that the recommended dose of tafamidis is 61 mg once daily (bioequivalent to 80 mg tafamidis meglumine). The Economics Sub Committee (ESC) noted that, while the safety profile of the two dosing regimens appeared to be broadly similar, this was based on a relatively small clinical trial exposure. The ESC requested that, in light of the similar efficacy between the 20 mg and 80 mg doses, the sponsor provide further information as to why it had not sought TGA registration and PBS listing of the 20 mg once daily dose that was also used in the trial. The pre-PBAC response stated that the 80 mg dose was associated with: more favourable results for the outcome of NT-proBNP; a greater degree of transthyretin tetramer stabilisation; and a more favourable result for the outcome of all-cause mortality when adjusted for age. The

PBAC noted that all-cause mortality was numerically better for the 20mg dose (27.3%) compared to the 80mg dose (30.7%) at 30 months. The PBAC also noted that a number of other results (e.g. cardiovascular mortality, cardiovascular hospitalisations) had point estimates that were numerically in favour of the 20 mg dose over the 80 mg dose. Hence, the PBAC remained unconvinced that there was any evidence to support the dose of 80 mg rather than 20 mg.

- 3.5 The targeted patient population identified through the requested restriction is broader than the inclusion criteria in the key clinical trial supporting the submission, the ATTR-ACT trial, which required patients to have ≥ 1 prior hospitalisations for heart failure or clinical evidence of heart failure requiring treatment with a diuretic, and excluding patients with NYHA class IV heart failure, and patients with reduced functional capacity (i.e. patients unable to achieve ≥ 100 metres on the 6MWT). Overall, the requested restriction included a broader section of the ATTR-CM population, including patients with a greater burden of more severe heart failure. The Pre-Sub-Committee Response (PSCR) argued that this was an appropriate extrapolation of the trial, but the ESC and DUSC considered that the eligibility criteria should match the clinical trial more closely and that variation from this would likely lead to reduced overall benefit and hence a higher ICER.
- 3.6 As such, the ESC and the PBAC considered that the requested restriction could be simplified, and more closely aligned with the ATTR-ACT trial inclusion/exclusion criteria by requiring patients to have:
- evidence or history of heart failure (history of ≥ 1 hospitalisations for heart failure, or clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement); AND
 - NYHA Class I-III; AND
 - echocardiography showing an end-diastolic interventricular septal wall thickness ≥ 12 mm; AND
 - transthyretin precursor protein identified by either:
 - Histological confirmation by immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry; OR
 - Grade 2 or 3 on bone scintigraphy with technetium-labelled radioactive tracer and negative results for monoclonal protein on all three tests (serum and urine immunofixation and electrophoresis, and serum free light chains).
- 3.7 The requested restriction included all patients with ATTR-CM regardless of severity of heart failure (i.e. New York Heart Association (NYHA) classifications I – IV), which is a broader population than the population in the key clinical trial (NYHA class I-III). The PSCR stated that the sponsor was ‘not opposed to restriction of initiation of tafamidis to patients with Class I-III symptoms with the endorsement of clinicians and other relevant stakeholders’. The ESC and PBAC considered that the restriction should exclude patients with NYHA Class IV and eGFR $<25\text{mL}/\text{min}/1.73\text{m}^2$ to align more closely with the key clinical trial.

- 3.8 The continuing restriction proposed in the submission did not include criteria for measuring response or a stopping rule. DUSC considered that the lack of discontinuation criteria could lead to patients receiving life-long treatment at substantial cost, which may not realise a clinical benefit. The ESC and PBAC considered that patients who progress to NYHA Class IV, or who receive a heart or liver transplant or an implanted cardiac ventricular assist device should be required to discontinue tafamidis in line with the ATTR-ACT trial exclusion criteria.
- 3.9 The sponsor submitted an application to the Medicare Services Advisory Committee (MSAC) requesting MBS listing of bone scintigraphy for the diagnosis of ATTR-CM, as a codependent submission with the tafamidis submission to the PBAC (MSAC Public Summary Document 1584, 76th MSAC meeting 1-2 August 2019). MSAC noted that the proposed new services can already be performed under existing MBS bone study items (61446 and 61449) and so considered that a HTA assessment of their safety and effectiveness was not necessary. MSAC advised the PBAC that the diagnostic performance of cardiac scintigraphy via bone studies should be considered acceptably similar to endomyocardial biopsy for the purposes of determining eligibility for tafamidis for the treatment of ATTR-CM. The ESC noted that this was in the context of the algorithm for the diagnosis of ATTR-CM, which the ESC considered would also include negative screens for monoclonal protein.
- 3.10 The clinical trial (ATTR-ACT) required endomyocardial biopsy to confirm the diagnosis of ATTR-CM. Eligibility under the proposed restriction uses a combination of screening for monoclonal protein, tissue biopsy for transthyretin protein (immunohistochemistry or mass spectrometry) and bone scintigraphy using one of three different technetium-based bone scintigraphic techniques. Data supporting the use of bone scintigraphy (Gillmore et al 2016) indicates a positive predictive value of 99 to 100% for the diagnosis of ATTR-CM using the criteria proposed in the restriction. However, the ESC and PBAC noted that these data were derived from referrals to a specialised amyloid centre and may not be reproducible in non-specialised centres. The ESC and PBAC considered that this could potentially lead to over-diagnosis, especially as use of bone scintigraphy in this clinical situation is evolving. This would be especially of potential concern in centres which had lower levels of experience with bone scintigraphy for the diagnosis of amyloid. The PBAC also noted that the interpretation of bone scintigraphy was somewhat subjective and felt that there may be considerable advantages in having a more uniform approach to interpretation of the bone scintigraphy tests.
- 3.11 The PBAC considered that the treatment criteria in the initial treatment setting should limit use to patients who are treated by a specialist cardiologist. The PBAC considered that, in the continuing setting, treatment in consultation with a specialist cardiologist would also be appropriate.
- 3.12 The submission requested a grandfather restriction. The submission indicated that approximately less than 10,000 patients will require grandfather access. The Secretariat noted that a grandfather restriction may not be required as patients

receiving non-PBS subsidised tafamidis would be eligible for tafamidis through the initial restriction (provided they meet the PBS criteria) given that no timeframe was specified regarding the recency of test results. The PBAC agreed that any grandfather clause would have to be aligned with the initial restriction.

- 3.13 DUSC considered there is a risk of use outside the intended restriction in patients with minimal symptoms who meet imaging criteria for ATTR-CM, particularly as asymptomatic amyloid deposition increases in prevalence with age. The PBAC agreed with DUSC that there is a high risk of use outside the intended restriction.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 ATTR-CM is a rare, late onset, progressive disease, characterised by extracellular deposition of misfolded transthyretin (TTR) amyloid fibrils in the cardiac atrial and ventricular walls, and/or direct amyloid proteotoxicity (Siddiqi et al. 2018). Amyloid fibril deposition results in progressive increase in myocardial thickness, restrictive cardiomyopathy with diastolic dysfunction (with or without systolic dysfunction) and progressive heart failure (Donnelly and Hanna 2017; Mankad and Shah 2017). Fibril infiltration around cardiac conduction tissue may result in cardiac arrhythmias (e.g. atrial fibrillation), atrioventricular conduction defects or even sudden cardiac death.
- 4.2 ATTR-CM is related to either a wild TTR genotype (ATTRwt; most common), or an autosomal dominant, inherited or variant TTR genotype (ATTRm), and is most prevalent in males ≥ 60 years of age, with prevalence increasing with age (Siddiqi et al. 2018). Disease trajectory is heterogeneous between TTR genotypes in terms of organ involvement, age of onset, presentation and prognosis, while the ATTRm genotype also varies between mutations in terms of prevalence, pattern of organ involvement, prognosis, race and region.
- 4.3 In current clinical practice, diagnosis of ATTR-CM is frequently delayed until the presentation of progressive heart failure. Median survival after diagnosis in untreated patients has been estimated to be 2.5 years for ATTRm and 3.5 years for ATTRwt, with death most likely due to cardiovascular causes (cardiac arrhythmia, heart failure; Dungu et al. 2012; Maurer et al. 2017; Ruberg et al. 2012).
- 4.4 ATTR-CM is suspected in patients with heart failure with preserved ejection fraction (HFpEF) with left ventricular hypertrophy (end-diastolic wall thickness >12 mm), particularly in the presence of extracardiac manifestations of amyloidosis (e.g. bilateral carpal tunnel syndrome) or a family history of ATTR-CM. The submission proposed that diagnosis would then be confirmed by the absence of monoclonal protein, positive radionuclide imaging (bone scintigraphy studies) and/or endomyocardial biopsy (where diagnosis cannot be confirmed by less invasive tests). The submission acknowledged that increased use of scintigraphy in the Australian setting may increase early diagnosis of ATTR-CM and identify additional patients currently undiagnosed or misdiagnosed.

- 4.5 A recent review (Driggin and Maurer 2019) of the epidemiology of ATTR-CM reported studies identifying up to 40% of patients with HFpEF exhibiting ATTRwt at autopsy. In addition, the screening with scintigraphy of 120 hospitalised elderly patients with HFpEF and increased ventricular wall thickness >12 mm on echocardiography, showed 13% exhibited uptake consistent with ATTRwt cardiac amyloidosis (Gonzarles-Lopez et al. 2015).
- 4.6 The ESC considered there would be a considerable increase in patients diagnosed with ATTR-CM under the new clinical management algorithm and if tafamidis were available. The ESC also considered that some of these newly diagnosed patients may have more benign clinical courses and that the overall natural history of ATTR-CM may evolve with changing diagnostic paradigms. The pre-PBAC response argued that earlier diagnosis of ATTR-CM would result in a greater proportion of eligible patients being in lower NYHA classes, in whom tafamidis is more cost-effective. However, the PBAC considered that the overall impact of diagnosing patients significantly earlier in the clinical course of the condition was unknown.
- 4.7 Tafamidis is a novel, small molecule, first in class oral therapy that attaches to thyroxine binding sites on the TTR tetramer, inhibiting tetramer dissociation and destabilisation. This inhibits the amyloidogenesis of aggregation-prone misfolded monomers, reducing the amyloid related direct cellular toxicity (proteotoxicity) and extracellular amyloid fibril deposition that result in cardiac dysfunction (i.e. ATTR-CM).

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated standard management of the symptoms of ATTR-CM (diuretic and/or anti-arrhythmic medicines) as the main comparator. The main argument provided in support of this nomination was that tafamidis is a first-in-field disease modifying medicine for the treatment of ATTR-CM, and that there are no other pharmacological treatments available that reduce amyloid formation or deposition, and disease progression in ATTR-CM. The ESC considered that standard management of ATTR-CM was the appropriate comparator, but also considered that treatment with tafamidis would be concomitant with ongoing standard management in clinical practice.
- 5.2 The clinical management algorithm positions tafamidis as the only disease modifying agent available to patients, as an alternative to standard management alone. Standard management in ATTR-CM was not defined in the submission but is expected to be consistent with the management of restrictive cardiomyopathy (i.e. diuretics, anti-arrhythmics and management of conduction defects).
- 5.3 The submission acknowledged that heart transplant is also a disease modifying procedure for severe progressed ATTR-CM, but suggested this procedure is not commonly performed in Australian clinical practice due to organ donor shortages. The ESC noted that mechanical cardiac assist devices are also a potential treatment, either

as a bridge-to-transplant or as destination therapy, but are not disease modifying. The submission also noted that diflunisal, a long acting non-steroidal anti-inflammatory medicine, is a potential near market comparator. Diflunisal is not currently listed on the Australian Register of Therapeutic Goods, but is used (off-label) in some patients with ATTR-CM, despite the absence of clinical evidence supporting its efficacy and safety in this setting. The ESC considered that diflunisal was not an appropriate comparator and that it was reasonable not to include heart transplantation or mechanical assist devices as comparators.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (10), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. Comments from health care professionals described the benefits of using tafamidis early in the disease trajectory. Comments from consumers described the lack of current treatments and the high unmet need for effective treatments. The comments described the fear of disease progression given the poor prognosis, and the significant impact that symptoms (shortness of breath, fatigue) have on a patient's quality of life and ability to carry out day-to-day functions. Individuals highlighted the psychological burden of having had positive genetic testing for hereditary (variant) ATTR-CM and waiting for the disease to develop or watching the gradual decline in physical functioning in family members with the disease. Comments from a patient taking tafamidis described a range of benefits including an increase in quality of life.

Clinical trials

6.3 The submission was based on one randomised placebo controlled trial (ATTR-ACT) comparing tafamidis meglumine in combination with standard management to standard management alone, in patients with transthyretin amyloid cardiomyopathy with evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness ≥ 12 mm.

6.4 A claim of superior efficacy and non-inferior safety was made on the primary and secondary outcomes of all-cause mortality, cardiovascular hospitalisations, the six minute walk test (6MWT) and the Kansas City Cardiomyopathy Questionnaire – overall score (KCCQ-OS). Pre-specified subgroup analyses were presented by NYHA heart failure classification and TTR genotype for key outcomes.

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6.5 The submission also presented preliminary results for patients who completed the ATTR-ACT trial and continued into Study B3461045 (N≈2000; an ongoing, long term, open label, safety study of tafamidis meglumine 20 mg and 80 mg; patients receiving placebo were randomised 1:2 to tafamidis meglumine 20 mg or 80 mg treatment arms). Evaluation of Study B3461045 could not be conducted due to insufficient information available in the submission and the published literature.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ATTR-ACT (B3461028) (NCT01994889)	A multicentre, international, phase 3, double-blind, placebo-controlled, randomized study to evaluate the efficacy, safety, and tolerability of daily oral dosing of tafamidis meglumine (PF-06291826) 20 mg or 80 mg in comparison to placebo in subjects diagnosed with transthyretin cardiomyopathy (TTR-CM). Maurer MS et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. Grogan M et al. Efficacy of tafamidis in patients with hereditary or wild-type transthyretin amyloid cardiomyopathy: further results from the ATTR-ACT Trial. Journal of heart and lung transplantation, 2019, 38(4):S204.	Report date: 28 August 2018 <i>New England Journal of Medicine</i> , 2018; 379(11): 1007-1016. <i>Journal of Heart and Lung Transplantation</i> , 2019, 38(4):S204.
B3461045 (extension study)	Elliot P et al. Interim analysis of data from a long-term, extension trial of tafamidis meglumine in patients with transthyretin amyloid cardiomyopathy (ongoing).	<i>European Heart Journal</i> , 2019: 40(Supplement 1, October 2019), 1169.

Source: Table 2.2.1, p.47 of the submission.

6.7 The key features of the trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
ATTR-ACT	Tafamidis meglumine 20 mg (N=88); Tafamidis meglumine 80 mg (N=176); Placebo (N=177)	R, DB, PC, MC, 30 months ^a	Unclear	18-90 years, ATTR-CM with cardiovascular involvement ^b	All-cause mortality, cardiovascular mortality, cardiovascular hospitalisation, 6MWT, KCCQ-OS, EQ-5D-3L	All-cause mortality (best supportive care arm); cardiovascular hospitalisation; treatment discontinuation; utilities
B3461045 (extension study) ^c	Continuing tafamidis (N=170); Switch to tafamidis (N=82);	30 months ^a (ongoing)	NK	NR	All-cause mortality, cardiovascular hospitalisation	All-cause survival (tafamidis arm)

Source: Section 2.4 of the submission; Elliot (2019).

Abbreviations: 6MWT, six minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; DB, double blind; EQ-5D, European quality of life 5 dimension questionnaire; KCCQ, Kansas City Cardiomyopathy Questionnaire; MC, multi-centre; NK, not known; NR, not reported; PC, placebo controlled; R, randomised.

^a ATTR-ACT treatment phase duration. Median duration of follow up was not reported. The B3461045 extension study is intended to provide at least an additional 30 months of data, but is ongoing.

^b Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness ≥ 12 mm.

^c Study features based on preliminary results published in conference poster presentation, for patients continuing from ATTR-ACT.

- 6.8 The ATTR-ACT trial may be subject to attrition bias as larger proportions of patients allocated to the placebo arm of ATTR-ACT discontinued participation (30.5%) compared to patients allocated to tafamidis 80 mg (21.6%) and tafamidis 20 mg (15.9%), and larger proportions of patients discontinuing participation allocated to placebo (68.5%) were not explained (i.e. “no longer willing to participate”), compared to tafamidis 80 mg (44.7%) and tafamidis 20 mg (57.1%). Given no patients were lost to follow up at 30 months after randomisation, it was unclear if this impacted results. The PSCR noted that attrition in the active treatment arm is common in trials of medications that are effective.
- 6.9 The ATTR-ACT trial included patients with a confirmed diagnosis of ATTRwt or ATTRm genotype ATTR-CM, based on biopsy results. The ESC noted that bone scintigraphy was not used in the ATTR-ACT trial for diagnosis, but that reasonable evidence exists to support bone scintigraphy for this purpose. Patients also required a history of one or more hospitalisations for heart failure, or clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement. Patients were required to demonstrate a serum NT-proBNP concentration ≥ 600 pg/mL, and be able to complete > 100 metres on the 6 minute walk test at screening. Baseline demographic characteristics were similar between treatment arms, with a mean age of 73.3-75.2 years in a predominantly male (88.7-94.3%), Caucasian (77.3-85.2%) population. Patients with the ATTRwt genotype comprised approximately 75% of each treatment arm. The PBAC noted that the clinical trial design had aimed to recruit at least 30% subjects with the ATTRm genotype.
- 6.10 The PBAC considered that the ATTR-ACT trial may have been subject to selection bias. Smaller proportions of patients reported NYHA class III heart failure at baseline in the tafamidis 20 mg (26.1%) and 80 mg (31.3%) treatment arms (pooled 29.5%), compared to the placebo arm (35.6%), primarily in patients with the ATTRwt genotype (tafamidis 20 mg 15.9%; tafamidis 80 mg 19.9%; placebo 24.9%). The smaller proportions of patients in the tafamidis treatment arms with more severe NYHA class III heart failure at baseline compared to placebo, may have biased trial outcomes in favour of tafamidis.
- 6.11 The primary efficacy analysis in the ATTR-ACT trial was a Finkelstein-Schoenfeld prioritised pairwise comparison (a generalisation of the Wilcoxon rank-sum test) of all-cause mortality and frequency of cardiovascular related hospitalisations. The analysis was based on hierarchical pairwise comparisons between all patients by strata (ATTRm and ATTRwt genotypes; NYHA class I + II and NYHA class III), first by all-cause mortality (or duration of survival time if both dead), and then by cardiovascular related hospitalisations (if both alive at 30 months). The result of each comparison assigns a score of +1 (better), 0 (no difference) or -1 (worse) based on one of six possible scenarios. Scores are summed overall and by strata, to generate the test statistics (i.e. p-values). The use of the Finkelstein-Schoenfeld prioritised pairwise comparison provides a composite outcome in which a substantial treatment

difference in either or both of the included measures results in rejection of the null hypothesis (noting that the method provides prioritisation to all cause mortality) and should be interpreted in conjunction with the results of the individual component outcomes. The ESC considered this method of analysis was valid and appropriate in the context of a relatively small sample size.

Comparative effectiveness

6.12 Table 4 summarises time to all-cause mortality by tafamidis dose for the ATTR-ACT trial at 30 months (ITT). Figure 1 (below) shows the Kaplan-Meier plots of time to all-cause mortality by tafamidis dose and pooled tafamidis treatment arms versus placebo.

Table 4: Summary of all-cause mortality events for ATTR-ACT (ITT; randomisation to 30 months)

Events, n (%)	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
N	88	176	264	177
All-cause mortality events ^a	24 (27.3%)	54 (30.7%)	78 (29.5%)	76 (42.9%)
Total deaths	23 (26.1%)	46 (26.1%)	69 (26.1%)	72 (40.7%)
Heart transplants	1 (1.1%)	6 (3.4%)	7 (2.7%)	4 (2.3%)
Cardiac device implants	0	2 (1.1%)	2 (0.8%)	0
Censored ^b	64 (72.7%)	122 (69.3%)	186 (70.5%)	101 (57.1%)
Kaplan-Meier estimates of time to event (months) by Quartiles (95% CI)				
25%	26.0 (14.5, NE)	24.6 (18.6, NE)	25.9 (19.8, NE)	20.9 (17.1, 23.0)
50%	NE	NE	NE	NE (29.7, NE)
75%	NE	NE	NE	NE
Cox proportional hazard ratio vs placebo (95% CI)	0.715 (0.450, 1.137)	0.690 (0.487, 0.979)	0.698 (0.508, 0.958)	-

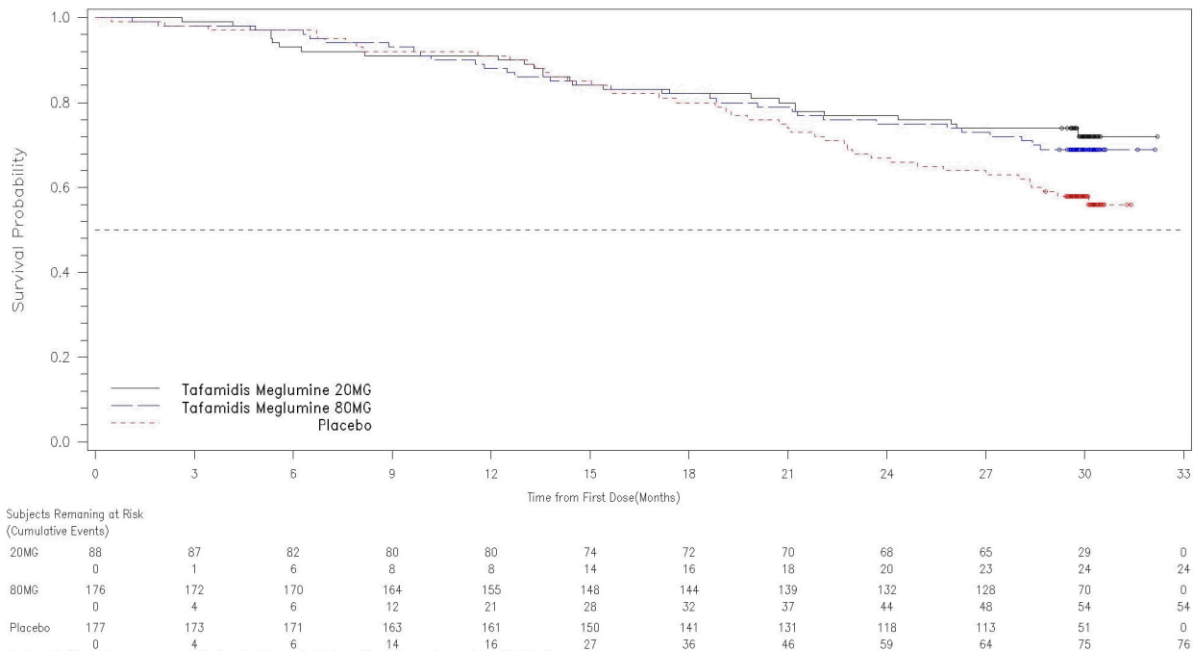
Source: Table 2.5.3, p.80 and Table 2.5.12, p.107 of the submission. Statistically significant results in bold.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; NE, not evaluable.

^a Heart transplant or implantation of a cardiac mechanical assist device handled as death.

^b Censored alive at time of analysis.

Figure 1: Kaplan-Meier plot of time to all-cause mortality for tafamidis by dose versus placebo in ATTR-ACT (ITT)



Source: Figure 15, p.128 of the ATTR-ACT Clinical Study Report.

Abbreviations: ITT, intention-to-treat.

Note: Heart transplant and implantation of a cardiac mechanical assist device handled as deaths.

6.13 All-cause mortality was lower in the tafamidis 80 mg (30.7%) and pooled tafamidis (29.5%) treatment arms at 30 months compared to placebo (42.9%), with the Cox-proportional hazard ratios demonstrating a statistically significant reduction in the risk of death of 31.0% for tafamidis 80 mg and 30.2% for pooled tafamidis, relative to placebo. The observed treatment effect of tafamidis on all-cause mortality emerged after approximately 18 months of treatment, consistent with the slow, progressive disease trajectory of ATTR-CM.

6.14 Table 5 summarises cardiovascular mortality by tafamidis dose for the ATTR-ACT trial at 30 months (ITT). Figure 2 (below) show Kaplan-Meier plots of time to event for cardiovascular mortality by tafamidis dose and pooled tafamidis treatment arms versus placebo.

Table 5: Summary of time to cardiovascular mortality by tafamidis dose for ATTR-ACT (ITT; randomisation to 30 months)

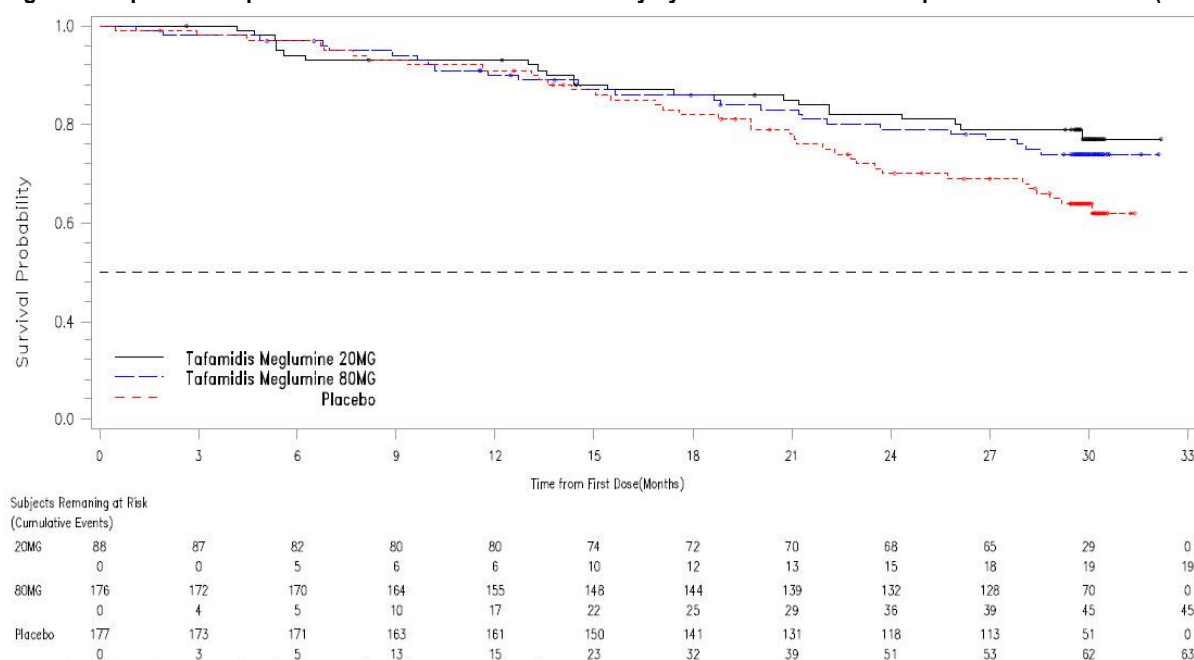
Cardiovascular mortality events, n (%)	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
N	88	176	264	177
Cardiovascular mortality events ^a	19 (21.6%)	45 (25.6%)	64 (24.2%)	63 (35.6%)
Cardiovascular deaths	18 (20.5%)	37 (21.0%)	55 (20.8%)	59 (33.3%)
Heart transplants	1 (1.1%)	6 (3.4%)	7 (2.7%)	4 (2.3%)
Cardiac device implants	0	2 (1.1%)	2 (0.8%)	0
Censored ^b	69 (78.4%)	131 (74.4%)	200 (75.8%)	114 (64.4%)
Kaplan-Meier estimates of time to event (months) by Quartiles (95% CI)				
25%	NE (21.2, NE)	28.4 (21.3, NE)	29.8 (23.7, NE)	22.1 (18.8, 27.1)
50% & 75%	NE	NE	NE	NE
Hazard ratio vs placebo (95% CI)	0.678 (0.404, 1.139)	0.690 (0.470, 1.012)	0.691 (0.488, 0.980)	-

Source: Table 2.5.7, p.92 of the submission; Table 17, p.113 of the ATTR-ACT Clinical Study Report. Statistically significant results in bold. Abbreviations: CI, confidence interval; ITT, intention-to-treat; NYHA, New York Heart Association heart failure classification; TTR, transthyretin.

^a Heart transplant or implantation of a cardiac mechanical assist device handled as death.

^b Censored alive at time of analysis.

Figure 2: Kaplan-Meier plot of time to cardiovascular mortality by tafamidis dose versus placebo in ATTR-ACT (ITT)



Source: Figure 14, p.112 of the ATTR-ACT Clinical Study Report.

Abbreviations: ITT, intention-to-treat.

6.15 Cardiovascular mortality was lower in the tafamidis 20 mg (21.6%), tafamidis 80 mg (25.6%) and pooled tafamidis (24.2%) treatment arms at 30 months compared to placebo (35.6%), with the Cox-proportional hazard ratios demonstrating a statistically significant reduction in the risk of death of 30.9% for the pooled tafamidis treatment arms relative to placebo. There was no statistically significant difference in time to event cardiovascular mortality between tafamidis 20 mg or tafamidis 80 mg compared

to placebo. As in all-cause mortality, the observed treatment effect of tafamidis on cardiovascular mortality emerged after approximately 18 months of treatment.

- 6.16 Kaplan Meier plots of all-cause mortality for the ATTR-ACT treatment period and B3461045 extension study, for those patients continuing treatment with tafamidis versus those patients switching from placebo to tafamidis showed a 36% reduction in all-cause mortality for patients continuing tafamidis (n=170 continuing, 88/264 events, 33.3%) versus patients switching from placebo to tafamidis (n=82 continuing, 89/177 events, 50.3%), at a median follow up of 36 months (HR 0.64, 95% CI [0.47, 0.85]).
- 6.17 Table 6 summarises the frequency of cardiovascular related hospitalisations by tafamidis dose for the ATTR-ACT trial from randomisation to 30 months (ITT).

Table 6: Summary of the frequency of cardiovascular hospitalisation events by tafamidis dose for ATTR-ACT (ITT; randomisation to 30 months)

Cardiovascular hospitalisation events	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
N	88	176	264	177
Patients experiencing events, n (%)	42 (47.5%)	96 (54.5%)	138 (52.3%)	107 (60.5%)
Mean (SD) cardiovascular hospitalisations per year ^a	0.976 (2.117)	1.010 (2.360)	0.999 (2.278)	0.884 (1.203)
Median (range) cardiovascular hospitalisations per year ^a	0 (0, 12.04)	0.397 (0, 21.49)	0.395 (0, 21.49)	0.403 (0, 7.23)
Frequency of cardiovascular hospitalisations (95% CI) ^b	0.464 (0.371, 0.581)	0.491 (0.421, 0.572)	0.475 (0.418, 0.540)	0.702 (0.617, 0.799)
Relative risk vs placebo (95% CI)	0.661 (0.511, 0.856)	0.699 (0.572, 0.855)	0.676 (0.564, 0.811)	-

Source: Table 2.5.4, p.81 and Table 2.5.13, p.107 of the submission. Statistically significant results in bold.

Abbreviations: CI, confidence interval; ITT, intention-to-treat; NYHA, New York Heart Association heart failure classification; SD, standard deviation; TTR, transthyretin.

^a Cardiovascular-related hospitalisations per year calculated as (patient's number of cardiovascular hospitalisations)/(duration on study in years).

^b Poisson regression analysis with treatment, TTR genotype, NYHA baseline classification (NYHA I & II; NYHA III), treatment-by-TTR genotype interaction, and treatment by NYHA baseline classification interaction terms as factors, adjusted for treatment duration.

- 6.18 Lower proportions of patients experienced cardiovascular hospitalisation events in the tafamidis 20 mg (47.5%) and tafamidis 80 mg (54.5%) treatment arms compared to placebo (60.5%). The median number of hospitalisations per year was similar between the tafamidis 80 mg and placebo arms. However, when estimates were reported as mean number of hospitalisations per year, patients in the placebo arm had similar or slightly lower events (0.884) compared to tafamidis treated patients (0.999 in the pooled population).
- 6.19 Comparisons between treatment arms based on a Poisson regression analysis with treatment, TTR genotype, NYHA baseline classification, treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors, and adjusted for treatment duration, showed the risk of cardiovascular hospitalisation was 33.9% lower for tafamidis 20 mg, 30.0% lower for tafamidis 80 mg and 32.4% lower for the pooled tafamidis arms compared to placebo. The reasons for

the differences in estimates between mean and median cardiovascular hospitalisations per year and frequency of cardiovascular hospitalisation was unclear.

- 6.20 Table 7 summarises the results of the primary outcome in the ATTR-ACT trial; the Finkelstein-Schoenfeld prioritised pairwise comparison of all-cause mortality and cardiovascular hospitalisation for tafamidis versus placebo (ITT).

Table 7: Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of cardiovascular hospitalisation for tafamidis versus placebo for ATTR-ACT (ITT)

	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
N	88	176	264	177
Number of subjects alive at 30 months, n (%) ^a	64 (72.7%)	122 (69.3%)	186 (70.5%)	101 (57.1%)
Average number/patient/year of cardiovascular hospitalisations at 30 months ^b	0.218	0.339	0.297	0.455
Finkelstein-Schoenfeld analysis versus placebo (p-value)	p = 0.0048	p = 0.0030	p = 0.0006	-

Source: Table 2.5.1, p.77 of the submission. Statistically significant results in bold.

Abbreviations: ITT, intention-to-treat.

^a Heart transplant or implantation of a cardiac mechanical assist device handled as death.

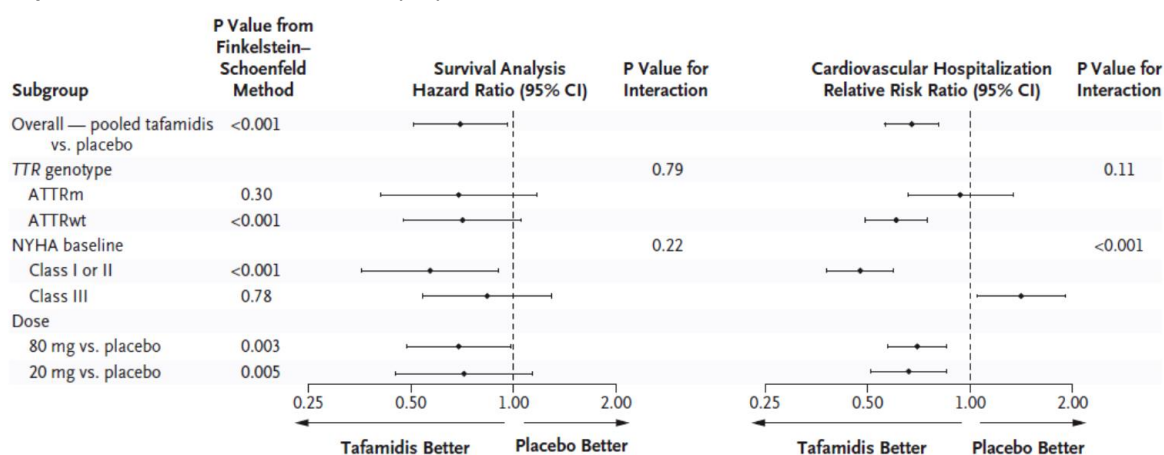
^b Calculated as [patient's number of hospitalisations] / [study duration in years] among those alive at 30 months.

- 6.21 In the primary outcome for the ATTR-ACT trial, the Finkelstein-Schoenfeld prioritised pairwise comparison of all-cause mortality and cardiovascular hospitalisations showed statistically significant results in favour of tafamidis 20 mg, tafamidis 80 mg and the pooled tafamidis treatment arm, versus placebo, suggesting a statistically significant difference between tafamidis and placebo in at least one or both outcomes. The average number of cardiovascular-related hospitalisations per patient per year amongst those alive at 30 months was lowest in patients treated with tafamidis 20 mg (0.218), compared to tafamidis 80 mg (0.339) and placebo (0.455). Similarly, the proportion of patients alive at 30 months was larger in the tafamidis 20 mg treatment arm (72.7%) compared to tafamidis 80 mg (69.3%) and placebo (57.1%).
- 6.22 A key secondary end point was the least squares mean change from baseline to month 30 in the distance walked during the 6MWT. The month 30 least squares mean change from baseline in distance walked for the pooled tafamidis and placebo groups was -54.87 (standard error: 5.07) and -130.55 (standard error: 9.80) metres, respectively. Tafamidis (pooled treatment arms) reduced the decline in the distance walked during the 6MWT as compared with placebo by approximately 75.7 metres (standard error: 9.24; P<0.001). In the ATTR-ACT trial, larger proportions of patients receiving placebo recorded incomplete or not properly administered 6MWT (24.7% and 29.5% respectively), compared to the tafamidis 20 mg (18.3% and 19.7%) and tafamidis 80 mg (14.6% and 17.4%) treatment arms (Table 5, p.75 of the Tafamidis Clinical Study Report). Given the likely variability between centres in 6MWT conduct and methodology (Giannitsi et al. 2019), and the larger proportions of placebo patients with incomplete or not properly administered tests in the ATTR-ACT trial, the 6MWT may not accurately reflect differences in patient functional capacity. The PSCR

recognised discrepancies in the administration of the 6MWT between centres, but claimed that this did not alter the differential benefit of the outcome.

- 6.23 Patients treated with tafamidis reported statistically significantly smaller mean reductions in the KCCQ-OS compared to placebo. However, scores were not consistent across all domains, and mean domain scores reported for symptom-stability and self-efficacy were not statistically significant.
- 6.24 Baseline mean EQ-5D-3L scores were similar between treatment arms (tafamidis pooled 0.802; placebo 0.800), with a larger decline in quality of life over 30 months observed in the placebo treatment arm (-0.14) compared to the pooled tafamidis treatment arms (-0.05; least squares mean difference favouring tafamidis of 0.09, 95% CI[0.05, 0.12]). EQ-5D-3L results by NYHA classification show substantial differences between NYHA classes, consistent with disease progression.
- 6.25 Figure 3 summarises the results of the subgroup analyses for all-cause mortality and cardiovascular hospitalisations with p-values by the Finkelstein-Schoenfeld methodology.

Figure 3: Summary of pre-specified subgroup analyses of all-cause mortality and cardiovascular related hospitalisations in the ATTR-ACT trial (ITT)



Source: Figure 2.6.1, p.128 of the submission.

Abbreviations: ATTRm, variant transthyretin amyloidosis; ATTRwt, wild type transthyretin amyloidosis; CI, confidence interval; ITT, intention-to-treat; NYHA, New York Heart Association classification; TTR, transthyretin.

These were stated to be pre-specified subgroups in Maurer et al, 2018.

- 6.26 Tests for treatment effect interaction indicate no statistically significant interaction by TTR genotype. However, interaction tests indicate that NYHA class is a treatment effect modifier for cardiovascular hospitalisation, with results indicating an increased risk of cardiovascular hospitalisation in patients with NYHA class III treated with tafamidis compared to placebo. The submission argued that the increased risk of hospitalisation was due to increased survival with tafamidis treatment in patients with severe heart failure. The submission did not provide any data to support this argument. Subgroup analyses provided in the submission suggest a small improvement in all-cause mortality in the NYHA III population which was not statistically significant (55.1% in the pooled tafamidis arm, versus 61.9% in the placebo

arm; HR: 0.84, 95% CI [0.54, 1.30]) although the trial was not designed to show a difference in this subgroup.

- 6.27 The PSCR stated that ‘some caution should also be exercised in the interpretation of the high rate of cardiovascular related hospitalisations observed in the NYHA Class III patient subgroup’. The PSCR argued that, when assessing hospitalisation rates by quartiles of 6MWT, rather than NYHA class (which the PSCR claimed was a more objective measure of functional capacity, without providing evidence to support this), the increased hospitalisation rate seen with tafamidis over placebo was argued to be attributable to a lower than expected hospitalisation rate in the placebo arm in the most severe 6MWT quartile (which the PSCR termed a “paradoxical pattern of behaviour in the placebo group”), rather than a higher rate in the tafamidis arm. The ESC considered that the increased rate of hospitalisations in patients with NYHA Class III treated with tafamidis compared to placebo was not adequately explained, and remained a significant concern because a large proportion of patients in clinical practice will be NYHA Class III (the submission estimated that 37% of patients treated with tafamidis would have NYHA Class III).
- 6.28 Table 8 summarises the mortality risk in the placebo arm of each of the subgroup populations.

Table 8: Mortality risk in the placebo arm of subgroup populations

Subgroup	All-cause mortality ^a	Cardiovascular mortality ^a
NYHA classification		
NYHA I/II	37/114 (32.5%)	32/114 (28.1%)
NYHA III	39/63 (61.9%)	31/63 (49.2%)
TTR genotype		
ATTRm	27/43 (62.8%)	22/43 (51.2%)
ATTRwt	49/134 (36.6%)	41/134 (30.6%)

Source: Table 2.6.2, p.140; Table 2.6.3, p.144; Table 2.6.7, p.157; Table 2.6.8, p.161 of the submission

^a Heart transplant or implantation of a cardiac mechanical assist device handled as death.

Abbreviations: ATTRm, variant transthyretin amyloidosis; ATTRwt, wild type transthyretin amyloidosis; NYHA, New York Heart Association heart failure classification; TTR, transthyretin.

- 6.29 Mortality data from the individual NYHA subgroups indicate that patients with NYHA class III had a higher baseline risk of all-cause mortality compared to patients with NYHA class I/II (61.9% versus 32.5%, respectively). Similarly, patients with NYHA class III had a higher baseline risk of cardiovascular mortality compared to patients with NYHA class I/II (49.2% versus 28.1%, respectively).
- 6.30 Mortality data from the individual genotype subgroups indicate that patients with ATTRm had a higher baseline risk of all-cause mortality compared to patients with ATTRwt (62.8% versus 36.6%, respectively). Similarly, patients with ATTRm had a higher risk of cardiovascular mortality compared with patients with ATTRwt (51.2% versus 30.6%).
- 6.31 The subgroup analyses indicate that the baseline risk of death varies substantially between subgroups. Therefore, even if constant relative treatment effects can be

assumed between NYHA classes and TTR genotypes, the absolute benefit of tafamidis treatment will vary substantially between subgroups.

Comparative harms

6.32 Table 9 summarises the proportions of patients experiencing key treatment emergent adverse events in the ATTR-ACT trial.

Table 9: Summary of key treatment emergent adverse events in the ATTR-ACT trial (safety population)

Patients with events	Tafamidis 20 mg	Tafamidis 80 mg	Tafamidis pooled	Placebo
N	88	176	264	177
Number of events	1036	2138	3174	2463
Patients reporting ≥ 1 treatment emergent adverse events				
Any adverse events (AEs)	87 (98.9%)	173 (98.3%)	260 (98.5%)	175 (98.9%)
Treatment related adverse events	34 (38.6%)	79 (44.9%)	113 (42.8%)	90 (50.8%)
Serious adverse events (SAEs)	54 (61.4%)	110 (62.5%)	164 (62.1%)	114 (64.4%)
Treatment related SAEs	2 (2.3%)	3 (1.7%)	5 (1.9%)	4 (2.3%)
Discontinuations related to AEs	16 (18.2%)	40 (22.7%)	56 (21.2%)	51 (28.8%)
Deaths during study period	14 (15.9%)	25 (14.2%)	39 (14.8%)	38 (21.5%)

Source: Table 2.5.16, p.113 of the submission.

Abbreviations: AEs, adverse events; ATTRm, variant (mutated) transthyretin amyloidosis; ATTRwt, wild type transthyretin amyloidosis; SAEs serious adverse events.

^a Median duration of follow-up in the ATTR-ACT trial was not reported in the submission or Clinical Study Report.

6.33 The proportions of patients reporting events was similar between the tafamidis and placebo treatment arms. Smaller proportions of patients reported treatment related adverse events in the tafamidis 20 mg treatment arm (38.6%) compared to tafamidis 80 mg (44.9%) and placebo (50.8%). Larger proportions of patients receiving placebo (28.8%) reported adverse events resulting in discontinuation compared to tafamidis (18.2-22.7%). Death due to unknown causes or unrelated to ATTR-CM were similar between treatment arms.

6.34 Table 10 summarises common treatment emergent adverse events reported in the ATTR-ACT trial.

Table 10: Summary of the most common treatment emergent adverse events reported in the ATTR-ACT trial

	Tafamidis 20 mg	Tafamidis 80 mg	Placebo
Treatment related adverse events in ≥ 5% of patients			
Gastrointestinal disorders	3 (3.4%)	22 (12.5%)	26 (14.7%)
Diarrhoea	2 (2.3%)	14 (8.0%)	18 (10.2%)
Nausea	1 (1.1%)	10 (5.7%)	10 (5.6%)
Infections and infestations	5 (5.7%)	4 (2.3%)	8 (4.5%)
Urinary tract infection	5 (5.7%)	4 (2.3%)	8 (4.5%)
Any treatment emergent adverse events reported by ≥ 15% of patients			
Cardiac failure	30 (34.1%)	46 (26.1%)	60 (33.9%)
Falls	27 (30.7%)	43 (24.4%)	41 (23.2%)
Atrial fibrillation	16 (18.2%)	35 (19.9%)	33 (18.6%)
Peripheral oedema	17 (19.3%)	30 (17.0%)	31 (17.5%)
Fatigue	16 (18.2%)	29 (16.5%)	33 (18.6%)
Dyspnoea	21 (23.9%)	29 (16.5%)	55 (31.1%)
Pain in extremity	6 (6.8%)	27 (15.3%)	20 (11.3%)
Constipation	14 (15.9%)	26 (14.8%)	30 (16.9%)
Dizziness	17 (19.3%)	25 (14.2%)	37 (20.9%)
Diarrhoea	10 (11.4%)	22 (12.5%)	39 (22.0%)
Cardiac failure congestive	17 (19.3%)	22 (12.5%)	33 (18.6%)
Cough	16 (18.2%)	21 (11.9%)	30 (16.9%)
Nausea	9 (10.2%)	20 (11.4%)	36 (20.3%)
Fluid overload	13 (14.8%)	19 (10.8%)	29 (16.4%)
Gout	10 (11.4%)	18 (10.2%)	29 (16.4%)
Acute kidney injury	12 (13.6%)	17 (9.7%)	29 (16.4%)
Urinary tract infection	9 (10.2%)	16 (9.1%)	27 (15.3%)

Source: Table 2.5.17, pp.114-116 of the submission.

6.35 The most common treatment related adverse events reported in the tafamidis 80 mg or placebo treatment arms were gastrointestinal disorders (diarrhoea and nausea), infections and infestations, and urinary tract infections. The most commonly reported treatment emergent adverse events reported by patients treated with tafamidis 20 mg and tafamidis 80 mg were cardiac failure (34.1%; 26.1%), falls (30.7%; 24.4%), atrial fibrillation (18.2%; 19.9%), dyspnoea (23.9%; 16.5%), peripheral oedema (19.3%; 17.0%), fatigue (18.2%; 16.5%), and pain in extremity (6.8%; 15.3%).

6.36 Similar events were commonly reported in the placebo arm (cardiac failure 33.9%, dyspnoea 31.1%, falls 23.2%, atrial fibrillation 18.6%, fatigue 18.6%, cardiac failure congestive 18.6%, peripheral oedema 17.5%), in addition to diarrhoea (22.0%), dizziness (20.9%), nausea (20.3%), pleural effusion (18.1%), constipation (16.9%), fluid overload (16.4%), gout (16.4%), acute kidney injury (16.4%), and urinary tract infection (15.3%).

Benefits/harms

6.37 On the basis of direct comparison evidence presented in the submission, for every 100 patients treated for 30 months with tafamidis meglumine 80 mg in combination with standard treatment, in comparison with standard treatment alone:

- Approximately 12 fewer patients will experience an all-cause mortality event.

- Approximately 10 fewer patients will experience a cardiovascular mortality event.
- Approximately 6 fewer patients will experience cardiovascular related hospitalisation.
- Approximately 6 fewer patients will experience a treatment related adverse event.
- Approximately 2 fewer patients will experience a serious adverse event.

Clinical claim

6.38 The submission described tafamidis 61 mg, in combination with standard management, as superior in terms of effectiveness and non-inferior in terms of safety compared to standard management alone. The ESC considered that the claim of superior effectiveness and non-inferior safety may be reasonable but considered that the claim was based on a relatively small clinical trial which had a potential risk of attrition and selection bias, and a heterogeneous population with substantial differences in baseline risks and a very limited safety dataset.

6.39 Further, the ESC considered that the magnitude of the incremental benefit of tafamidis in the requested PBS population was uncertain given:

- It is unclear whether the distribution of NYHA classes from the ATTR-ACT trial will be applicable to the Australian setting. Based on estimates from the sponsor commissioned survey, nearly half of the population expected to be treated with tafamidis would have either Class III (37%) or Class IV (11%) heart failure (compared with 32% and 0% in the ATTR-ACT trial, respectively). In addition, the ESC considered that likely changes in the diagnostic algorithm and likely increases in the diagnosis of ATTR-CM (potentially in patients with less severe disease) will affect the distribution of NYHA classes among patients with ATTR-CM and hence on the overall benefit to be expected with tafamidis.
- The ESC considered that the clinical benefits of tafamidis appear greater in patients with NYHA Class I/II than in those with NYHA Class III. Subgroup data from the ATTR-ACT trial suggest that extent of disease may be a treatment effect modifier, with an increase in hospitalisations and an uncertain impact on survival with tafamidis treatment in NYHA Class III patients.
- No clinical data were provided to support the use of tafamidis in NYHA Class IV patients.
- The absolute benefit of tafamidis treatment in different patient populations is uncertain, given that the baseline risk appears to vary substantially between NYHA classes and TTR genotypes. In addition, it is unclear if ATTRm phenotypes in the ATTR-ACT trial are applicable to the Australian setting. Though the PSCR compared the ATTRm mutations reported in the ATTR-ACT trial with a study conducted at the Westmead Amyloidosis Centre, the study was not provided and could not be located.

- 6.40 The PBAC considered that the claim of superior efficacy was reasonable and adequately supported by the data, but agreed with the ESC that the magnitude of the benefit in the proposed population was highly uncertain.
- 6.41 The PBAC considered that the clinical safety dataset was small and inadequate to make a claim of non-inferior safety.

Economic analysis

- 6.42 The submission presented a modelled economic evaluation of tafamidis compared to best supportive care for the treatment of patients with ATTR-CM. The economic evaluation was based on a direct randomised trial (ATTR-ACT) and extension study with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.
- 6.43 The poor documentation of many variables (transitions, utilities and costs) made it difficult to evaluate the economic model.

Table 11: Summary of model structure, key inputs and rationale

Component	Description
Type of analysis	Cost-effectiveness analysis; cost-utility analysis
Outcomes	Life years; quality adjusted life years
Time horizon	20 years
Methods used to generate results	Markov state transition model
Treatments	Tafamidis versus best supportive care
Health states	Two health states (alive and dead)
Cycle length	6 months (with half-cycle correction)
Patient characteristics	Distribution of patients across NYHA classes based on baseline values from the ATTR-ACT trial
Transition probability and event probability	<ul style="list-style-type: none"> • Transition probabilities for survival in the best supportive care arm were estimated by fitting a Gompertz curve to ATTR-ACT trial data. • Transition probabilities for survival in the tafamidis arm were estimated by fitting a gamma curve to ATTR-ACT trial and extension study data. • The probability of having a cardiovascular hospitalisation was estimated from post-hoc analyses of ATTR-ACT data by treatment arm and duration of exposure within each NYHA class. The probability of cardiovascular hospitalisation was assumed to remain constant over time. • The probability of discontinuation in the tafamidis arm was estimated by fitting a log normal curve to ATTR-ACT data.
Health related quality of life	Utilities based on a post-hoc reanalysis of EQ-5D-3L data (UK weights) from the ATTR-ACT trial by treatment arm and NYHA class. No additional disutility assumed for cardiovascular hospitalisation.
Costs	<ul style="list-style-type: none"> • Diagnostic costs were estimated based on expert advice on health resource use from a sponsor-commissioned physician survey. • Cardiovascular hospitalisation costs estimated as the weighted average of 98 cardiovascular-related AR-DRG items, i.e. not related to CVD hospitalisations observed in the trial. • Disease management costs were estimated from published studies (Ademi 2014, Ford 2012). • Terminal care costs were estimated based on the assumption that half of all deaths would be preceded by a cardiovascular-related hospitalisation, which the ESC considered would double-count some hospitalisation costs.
Discount rate	5% for costs and outcomes
Software package	Microsoft Excel

Source: Table 3.1.1 (p 180-181) of the submission

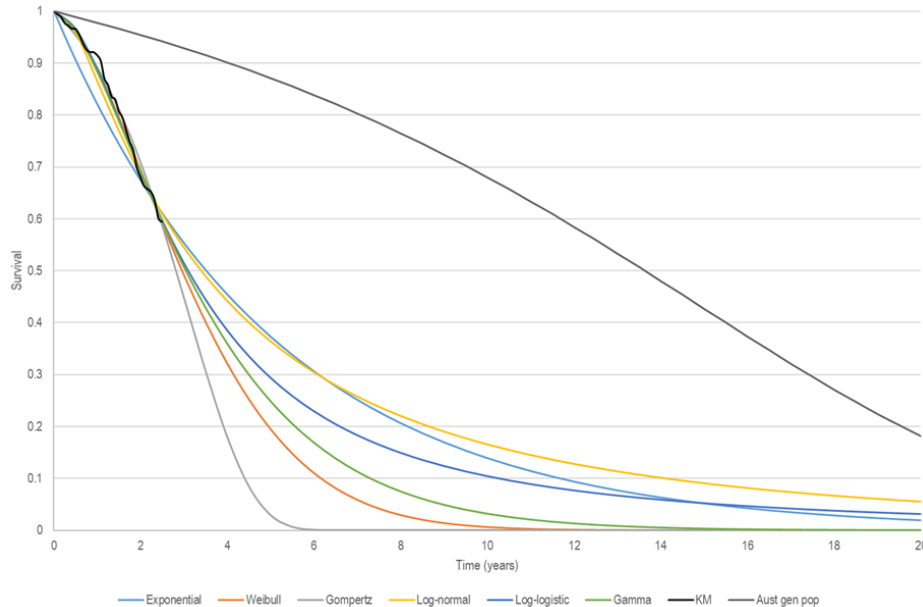
- 6.44 Prior to entering the economic model, patients with suspected ATTR-CM undergo a screening phase using the proposed testing algorithm. The submission estimated that 171 patients would be treated with tafamidis for every 1,000 individuals screened. The costs of the screening phase were applied as added costs to the tafamidis treatment arm in the economic evaluation.
- 6.45 Treated patients begin the model in the alive state. During each six-month cycle, patients can remain alive or die. The submission modelled transitions between the two health states (alive/dead) independently of cardiovascular hospitalisation events and independently of treatment status (on/off treatment).
- 6.46 Patients who are alive may remain event-free or experience a cardiovascular hospitalisation in each cycle. Cardiovascular hospitalisations were not linked to mortality in the economic model. The commentary and the ESC considered that the implicit assumption that all cardiovascular hospitalisations were non-fatal was

inappropriate as the cardiovascular hospitalisation rates reported in the ATTR-ACT trial included fatal and non-fatal events. A constant probability of hospitalisation was applied over the duration of the model, which was inappropriate as cardiovascular hospitalisations would generally be expected to increase with age and duration of disease. The pre-PBAC response argued that cardiovascular hospitalisations were not included as transition states and were only 'included to track relevant costs'. The PBAC considered that the modelling approach did not adequately incorporate the impact of cardiovascular hospitalisations and the likely progressive nature of the condition wherein cardiovascular hospitalisations would generally be expected to increase with age and duration of disease.

- 6.47 Additionally, patients in the tafamidis arm may discontinue drug treatment in each cycle. The treatment discontinuation estimates were only applied to drug costs, and had no impact on survival or cardiovascular hospitalisations. This was inappropriate as the implicit association between clinical outcomes and discontinuations observed in the trial is unlikely to be maintained over time. A higher proportion of modelled patients discontinue over time (the majority of patients have discontinued therapy by 11 years) and spend longer durations without therapy (where they are not accruing drug costs but are deriving treatment benefit). The pre-PBAC response argued that the efficacy results from ATTR-ACT, upon which the model were based, were analysed as intention-to-treat, and hence the benefits observed took into account treatment discontinuation. However, the PBAC considered that while this may be reasonable for the 30 month trial period, the implicit association between clinical outcomes and discontinuations observed in the trial is unlikely to be maintained over time.
- 6.48 The model assumed that patients remain in the same NYHA class over the duration of the model, which the ESC considered was inappropriate as it did not capture the progressive nature of ATTR-CM. The ESC considered that the overall impact of not explicitly modelling disease progression was unclear as: (a) on one hand, it may favour tafamidis as it does not capture the reduced utilities and increased treatment costs associated with progression during the additional survival period; but (b) on the other hand it may favour best supportive care as it does not capture the potential reduction in relative progression in the tafamidis arm. The pre-PBAC response argued the model applied overall survival data from ATTR-ACT, which implicitly included changes in NYHA class within the trial period. The pre-PBAC response further argued that if the model had allowed for movement of patients between NYHA classes, the survival data would not have been applicable. However, the PBAC considered that the model had not adequately captured the impact of the progressive nature of the condition beyond the trial period.
- 6.49 The submission derived survival estimates based on parametric survival functions fitted to Kaplan-Meier estimates of survival in the ATTR-ACT trial and extension, censored for transplantation/implantation events. The observed and extrapolated overall survival curves for best supportive care and tafamidis are shown in the figures below. The figures also include the survival curve for the general Australian

population, based on a population aged 74 years, with 90.2% male (consistent with the ATTR-ACT trial).

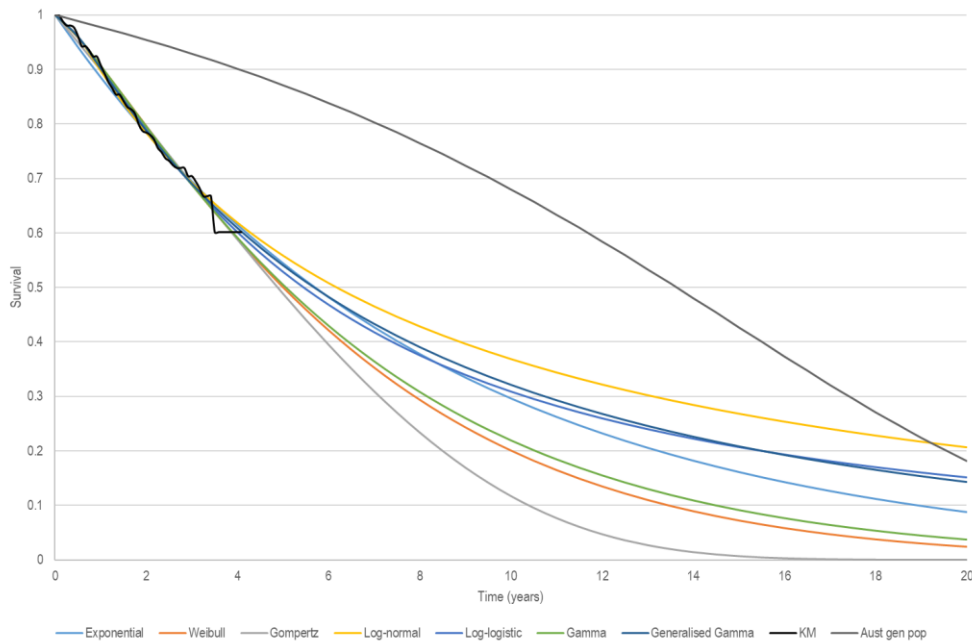
Figure 4: Observed (ATTR-ACT trial) and extrapolated overall survival curves for best supportive care



Source: Constructed during the evaluation using 'Utilisation-and-cost-model-tafamidis-final' spreadsheet provided with the submission
Abbreviations: Aust gen pop, Australian general population survival; KM, Kaplan Meier
Note: Death events censored for transplantation/implantation. Australian population survival from ABS life tables, age 74 years, 90.2% male.

6.50 For the best supportive care arm, the submission claimed that the log-normal, log-logistic and exponential curves were not clinically plausible as they predicted long-term survival that exceeded life expectancy estimates for the general population. However, the ESC noted that this did not occur within the 20 year model time horizon, as shown in the figure above. The submission claimed that of the remaining survival functions, the Gompertz function was the most appropriate as it predicted clinically relevant survival for the patient population and provided the best statistical fit. The ESC noted that the Gompertz function predicted markedly shorter survival than any of the other functions. The Weibull, Gompertz, gamma and log-logistic functions provided very similar goodness-of-fit estimates but led to divergent extrapolated estimates.

Figure 5: Observed (ATTR-ACT trial and extension) and extrapolated overall survival curves for tafamidis



Source: Constructed during the evaluation using 'Utilisation-and-cost-model-tafamidis-final' spreadsheet provided with the submission

Abbreviations: KM, Kaplan Meier; Aust gen pop, Australian general population survival

Note: Death events censored for transplantation/implantation. Australian population survival from ABS life tables, age 74 years, 90.2% male.

6.51 For the tafamidis arm, the submission claimed that the gamma function was the most appropriate parametric model to estimate survival based on goodness-of-fit parameters. The submission argued that it was reasonable to use different survival functions for each modelled treatment arm as tafamidis is a disease-modifying treatment that is expected to change survival. The ESC considered this argument was not reasonable given the differences in model fit were small and the proportional hazards assumption between treatments did not appear to be violated. Further, the ESC considered that selecting the gamma function (which the submission used in the base case for the tafamidis arm) for both arms may be appropriate as in the best supportive care arm the AIC/BIC statistics were similar for the gamma and Gompertz functions and the gamma function does not result in survival estimates which appear to be overly conservative (i.e. too short).

6.52 The submission estimated cardiovascular hospitalisation probabilities based on post-hoc analyses of ATTR-ACT data by treatment arm and duration of exposure within each NYHA class. The post-hoc analyses could not be validated during the evaluation due to a lack of documentation. It was also unclear how the post-hoc analyses corresponded with data from the trial report which suggested considerably different cardiovascular hospitalisations frequencies for each treatment arm (shown in Table 12). For example, the ESC noted that the annual cardiovascular hospitalisation rate in NYHA Class III was higher in the tafamidis arm than the best supportive care arm in the ATTR-ACT trial (for both the adjusted and unadjusted rates), but the modelled rate was lower in the tafamidis arm than in the best supportive care arm (1.54 versus 1.62).

Table 12: Comparison of cardiovascular hospitalisation rates between the ATTR-ACT trial and post-hoc analyses

Characteristic	Annual cardiovascular hospitalisation rate		
	Unadjusted rate ¹ ATTR-ACT	Adjusted rate ² ATTR-ACT	Modelled rate Post-hoc analyses
Tafamidis			
NYHA class I/II	0.490	0.3378	0.5096
NYHA class III	2.212	0.9722	1.5336
Alive health state	0.999	0.4750	0.8532
Best supportive care			
NYHA class I/II	0.823	0.7091	0.7142
NYHA class III	0.993	0.6924	1.6162
Alive health state	0.884	0.7025	1.0026

Source: Table 2.5.4 (p 80), Table 2.6.9 (p 161), Table 3.4.3 (p 197) of the submission

¹ Mean cardiovascular hospitalisations per year, calculated as (patient's number of cardiovascular hospitalisations)/(duration on study in years).

² Frequency of cardiovascular hospitalisations, calculated using Poisson regression analysis with treatment, TTR genotype, NYHA baseline classification (NYHA I & II; NYHA III), treatment-by-TTR genotype interaction, and treatment by NYHA baseline classification interaction terms as factors, adjusted for treatment duration.

- 6.53 The submission estimated the distribution of patients across NYHA classes based on baseline distribution in the ATTR-ACT trial, and this was used to inform utility values and costs in the base case (noting that patients remain in the same NYHA class over the duration of the model). It is unclear whether the distribution of NYHA classes from the ATTR-ACT trial will be applicable to the Australian setting, for example the distribution is likely to be affected by any changes in practices around testing for ATTR-CM over time. The evaluation conducted an economic analysis of patients with NYHA Class I/II and Class III disease which indicated substantially smaller incremental differences between treatments in patients with NYHA Class III (QALY difference versus best supportive care: 0.2098-0.4012) compared to Class I/II disease (QALY difference versus best supportive care: 3.5465). These analyses were derived from Kaplan-Meier estimates of survival in each of the subgroups and therefore reflect the baseline risk estimates and observed treatment effects in each of the populations (and also include the changes in costs and utilities). The PSCR considered there were errors in the analysis conducted by the evaluators and that the difference between NYHA Class I/II and Class III in incremental QALYs gained was much smaller. However, the ESC noted that the approach used in the PSCR only changed baseline NYHA class for the purpose of calculating utilities and hospitalisation and disease management costs, but assumed that survival was unchanged from the overall population (no difference in baseline risk or treatment effect).
- 6.54 The submission nominated a 20 year time horizon on the basis that this was appropriate to capture the majority of costs and benefits in an older population with ATTR-CM. A 20-year time horizon may not be appropriate given that the target population represents an older age group who are likely to have multiple co-morbidities (mean baseline age in the ATTR-ACT trial was approximately 74 years).
- 6.55 Key drivers of the economic model are summarised in the table below. The first three rows are structural issues.

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Table 13: Key drivers of the model

Description	Method/Value	Impact Base case ICER: \$more than \$200,000/QALY
Disease progression	<p>The submission assumed that patients remain in the same NYHA class over the duration of the model. The subgroup analyses conducted during the evaluation were also based on the same assumption due to the structural limitations of the model. However, this assumption was not consistent with either the clinical trial data nor the natural history of heart failure (which is a generally a progressive condition).</p> <p>If there are differences in disease progression, the overall direction of bias was unclear as the current model structure would favour:</p> <ul style="list-style-type: none"> • tafamidis by not representing the reduced utilities and increased treatment costs associated with progression during the additional survival period predicted for tafamidis. • best supportive care by not representing potentially reduced disease progression in the tafamidis arm. <p>The ESC considered that it was not possible to reliably test the impact of this within the current structure of the model, but noted that sensitivity analyses conducted by the evaluators indicated that as the proportion of patients with NYHA Class III increases, the ICER increases substantially (albeit these sensitivity analyses assume that NYHA class remains constant over time).</p>	High, direction unclear
Cardiovascular hospitalisations	<p>The implicit assumption that all cardiovascular hospitalisations were non-fatal was inappropriate as the cardiovascular hospitalisation rates reported in the ATTR-ACT trial included fatal and non-fatal events. A constant probability of hospitalisation was applied over the duration of the model, which was inappropriate as cardiovascular hospitalisations would generally be expected to increase with age.</p>	Moderate/High, favours tafamidis
Treatment effects and discontinuations	<p>The implicit assumption that the estimated treatment effect is maintained following treatment discontinuation was inappropriate. Increasing proportions of modelled patients discontinue over time, with the majority of patients having discontinued therapy by 11 years, and spend longer durations without therapy (where they are not accruing drug costs but are deriving treatment benefit). A sensitivity analysis was conducted which assumed no discontinuations over the course of the model. While this is a blunt approach, it indicates the sensitivity of the model to this assumption. (A more robust sensitivity analysis would be to apply the HR to the best supportive care arm for the proportion remaining on treatment, however this was not possible within the structure of the model.)</p>	High, favours tafamidis ICER = more than \$200,000/QALY if no discontinuations over the course of the model
Patient population	<p>The modelled population excludes NYHA Class IV patients (based on ATTR-ACT trial population) and, based on an analysis conducted during evaluation, the model outputs indicate substantially smaller incremental QALY gains for patients with NYHA Class III (QALY difference: 0.2098-0.4012) compared to Class I/II disease (QALY difference: 3.5465).</p> <p>The PSCR reported smaller but still significant differences in analyses by NYHA Class, based on a different method (which changed baseline NYHA class for the purpose of calculating utilities, hospitalisation and disease management costs; while the evaluation method also assumed changes in treatment effect and baseline risk between NYHA classes). The ESC considered that the methods for these analyses would need to be reviewed, e.g. for choice of extrapolation curves.</p>	Moderate/High, favours tafamidis

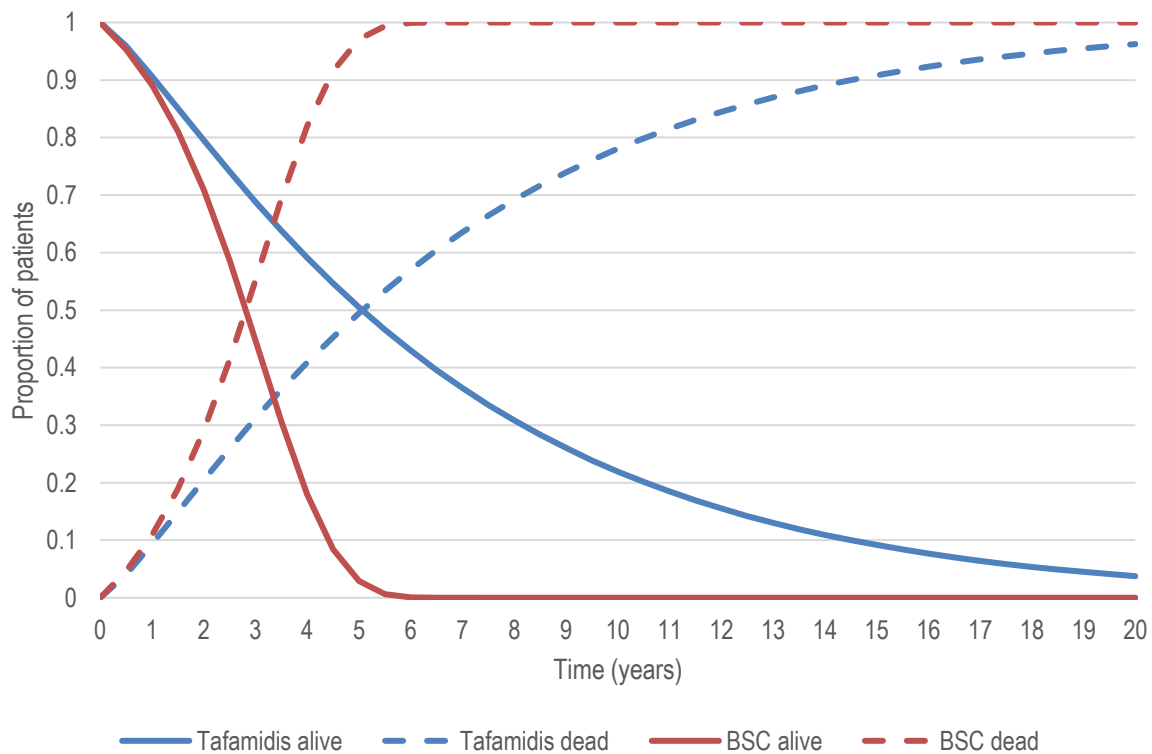
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Description	Method/Value	Impact Base case ICER: \$more than \$200,000/QALY
Survival extrapolation	The Weibull, Gompertz and gamma functions provided very similar goodness-of-fit estimates but led to divergent extrapolated estimates. Different parametric functions were used in the tafamidis and best supportive care arms. The ESC considered that it would be reasonable to use the same functions for the different treatment arms, and that the gamma distribution may be the most appropriate function to use in both arms.	High, favours tafamidis ICER = more than \$200,000/QALY if use gamma in both arms

Source: Constructed during the evaluation

6.56 The proportion of patients alive and dead in each treatment arm over the duration of the model is presented below.

Figure 6: Markov trace of the proportion of patients in each health state over time



Source: Constructed during the evaluation using 'Tafamidis economic model final' Excel spreadsheet provided with the submission
Abbreviations: BSC, best supportive care

6.57 The trace indicates rapid separation in survival between treatment arms with a median survival of approximately 2.5-3 years in the best supportive care arm and 5.0-5.5 years in the tafamidis arm. The model predicts all best supportive care patients will be dead within 7 years while the tafamidis treatment arm continues to have a long survival tail with 3.8% of patients alive at 20 years.

6.58 The results of the modelled economic evaluation are summarised below

Table 14: Results of the economic evaluation

Component	Tafamidis	Best supportive care	Increment
Costs ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
LYs	5.1789	2.5702	2.6087
Incremental cost per LY gained			\$ [REDACTED]
Costs ^a	\$ [REDACTED]	\$ [REDACTED]	\$ [REDACTED]
QALYs	3.7951	1.8267	1.9684
Incremental cost per QALY gained			\$ [REDACTED]

Source: Constructed during the evaluation based on Tafamidis economic model final Excel workbook

^a Includes correction of annual drug costs from \$ [REDACTED] to \$ [REDACTED]. This was accepted in the PSCR.

The redacted table shows ICERs in the range of more than \$200,000/QALY.

6.59 Based on the economic model, treatment with tafamidis was associated with a cost per QALY gained of more than \$200,000/QALY compared with best supportive care. The ESC considered that this cost-effectiveness estimate was unreliable given the major structural limitations of the model and the uncertain proportion of patients across NYHA classes.

6.60 Table 15 below compares the incremental outcomes of the model over the trial duration (30 months) with the outcomes over the 20 year time horizon.

Table 15: Comparison on modelled results within trial period and over 30 year time horizon

	Model results over trial duration (30 months)	Model results over 20 year time horizon	Proportion of incremental outcome in extrapolated period
Incremental cost	\$ [REDACTED]	\$ [REDACTED]	51.1%
Incremental LYs	0.1040	2.6087	96.0%
Incremental QALYs	0.1202	1.9684	93.9%
Incremental cardiovascular hospitalisations per patient	-0.2051	2.0672	109.9%

Source: Constructed during the evaluation using the 'Tafamidis economic model final' Excel spreadsheet provided with the submission
Abbreviations: LYs, life years; QALYs, quality adjusted life years

6.61 The majority of the incremental costs occur in the trial period, however the vast majority of incremental life years and QALYs accrue in the extrapolated period. Although best supportive care patients have a higher rate of cardiovascular hospitalisation than tafamidis patients in the key trial, the model predicted a higher number of cardiovascular hospitalisations in the tafamidis treatment arm due to the longer life expectancy with tafamidis treatment.

6.62 The results of key sensitivity analyses indicated that the model was sensitive to time horizon, survival extrapolations, patient population and treatment persistence.

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Table 16: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER
Base case	\$ [REDACTED]	1.9684	\$ [REDACTED]
Time horizon (base case: 20 years)			
10 years	\$ [REDACTED]	1.5689	\$ [REDACTED]
15 years	\$ [REDACTED]	1.8706	\$ [REDACTED]
Survival extrapolations (base case: best supportive care arm extrapolated using Gompertz function, tafamidis treatment arm extrapolated using gamma function)			
Best supportive care extrapolated using Weibull function	\$ [REDACTED]	1.6595	\$ [REDACTED]
Best supportive care extrapolated using gamma function (same function in each arm)	\$ [REDACTED]	1.4722	\$ [REDACTED]
Tafamidis extrapolated using Weibull function	\$ [REDACTED]	1.8680	\$ [REDACTED]
Tafamidis extrapolated using Gompertz function (same function in each arm)	\$ [REDACTED]	1.4958	\$ [REDACTED]
Patient population (base case: 68% NYHA Class I/II, 32% NYHA Class III)			
<u>Evaluation analysis:</u> All patients NYHA Class I/II (tafamidis gamma, lowest AIC/BIC that is clinically plausible; best supportive care Gompertz function, lowest AIC/BIC) ^a	\$ [REDACTED]	3.5465	\$ [REDACTED]
<u>Evaluation analysis:</u> All patients NYHA Class III (tafamidis Weibull, lowest AIC that is clinically plausible; best supportive care Weibull function, lowest AIC/BIC) ^a	\$ [REDACTED]	0.2098	\$ [REDACTED]
<u>PSCR analysis:</u> All patients NYHA Class III (Weibull for both arms)	\$ [REDACTED]	1.23	\$ [REDACTED]
<u>Evaluation analysis:</u> All patients NYHA Class III (tafamidis exponential, lowest BIC that is clinically plausible; best supportive care Weibull function, lowest AIC/BIC)	\$ [REDACTED]	0.4012	\$ [REDACTED]
<u>PSCR analysis:</u> All patients NYHA Class III (tafamidis exponential; best supportive care Weibull function)	\$ [REDACTED]	1.65	\$ [REDACTED]
Treatment persistence extrapolations (base case: discontinuations in the tafamidis treatment arm extrapolated using a lognormal function)			
Discontinuations extrapolated using exponential function	\$ [REDACTED]	1.9684	\$ [REDACTED]
No discontinuations from month 36 onwards (discontinuation curve same as survival curve)	\$ [REDACTED]	1.9684	\$ [REDACTED]
No discontinuations over the course of the model (discontinuation curve same as survival curve)	\$ [REDACTED]	1.9684	\$ [REDACTED]

Source: Table 3.9.1 (p 207) of the submission

^a Subgroup analyses conducted during the evaluation were based on Kaplan-Meier estimates of survival reported in the utilisation and cost Excel model (Section 4) and model fit parameters presented in the CEA model report for each of the NYHA subgroups.

The redacted table shows ICERs in the range of more than \$200,000/QALY.

6.63 The ESC considered that the key issues with the economic model were structural uncertainties and it was not possible to adequately test these given the limitations of the model presented. In particular, it was not possible to test the assumption that NYHA class was constant over time nor the independent modelling of survival, cardiovascular hospitalisations and treatment discontinuation (e.g. it was not possible to adequately test the assumptions that all cardiovascular hospitalisations were non-fatal or that the probability of cardiovascular hospitalisation would remain constant over time). While a sensitivity analyses had been conducted that assumed no

treatment discontinuations, the ESC acknowledged this did not reliably assess the impact of tafamidis discontinuations on both costs and outcomes.

- 6.64 The ESC considered that key sensitivity analyses include: use of gamma curves to model OS in both arms (increases ICER to more than \$200,000/QALY), and removal of treatment discontinuation (due to extrapolated benefits not reflecting treatment discontinuations, increases ICER to more than \$200,000/QALY).
- 6.65 The ESC considered that it may be more appropriate to model disease progression (e.g. by modelling progression through NYHA classes over time).

Drug cost/patient/year

- 6.66 Based on the proposed effective DPMQ (\$ ██████ for 30 days treatment) and 12.175 scripts per year (365.25/30), the annual costs for tafamidis would be \$ ██████ per patient.
- 6.67 Cost estimates do not include dose intensity but extrapolated drug costs in both the economic and financial estimates were modified based on treatment persistence (the probability of discontinuation in the tafamidis arm was estimated by fitting a log-normal curve to ATTR-ACT data).

Estimated PBS usage & financial implications

- 6.68 This submission was considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact of listing tafamidis on the PBS. Key inputs are summarised in the table below.

Table 17: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population, males ≥60 years	-	ABS population, by age and sex.	
Proportion of population with heart failure	60-64 yrs: 1.80% 85-100 yrs: 11.50%	Nicols et al. 2016.	Self-reported heart failure in Australian Health Survey 2011-2012. The study acknowledged issues with patient self-report. Estimates excluded patients who were resident in hospitals, nursing or convalescent homes. Other Australian studies suggest higher prevalence across age bands. Prevalence of heart failure likely to be underestimated.
Proportion of heart failure with HFpEF	34.26%	Chan et al. 2015.	Data from a US County in 1991, applied to 2014 Australian population estimates. Given the age of the data, based on a US population, the estimate is unlikely to reflect current practice in Australia and is a likely underestimate.
Proportion of HFpEF with amyloid deposition	60-64 yrs: 0.31% 85-100 yrs: 13.89%	Mohamed-Salem 2018.	Estimates, based on incidental findings in patients ≥75 years undergoing scintigraphy for oncologic (95.7%) and rheumatologic reasons (4.3%), are unlikely to be representative of the target population. Estimates used in younger populations could not be verified.
Proportion of ATTR-CM with HFrEF	Year 1: 30% Year 6: 5%	Expert opinion (physician)	Rapezzi et al, (2009) reported 40% of patients with HFrEF, reduced to 30% in the submission due to the sample size (n=15). Declining proportions over time were

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Data	Value	Source	Comment
		survey); Rapezzi et al, (2009).	assumed to reflect earlier diagnosis and reduced disease progression related to tafamidis treatment. The magnitude of effect on the reduction in disease progression from HFpEF to HFrEF was assumed, and may be overestimated. The number of patients with HFrEF is likely to be underestimated.
Proportion of ATTR-CM female	6.0%	Expert opinion (physician survey); Choi et al. 2009.	The sources used in the submission could not be located during the evaluation. Other studies, including the ATTR-ACT trial have found higher proportions of females with ATTR-CM, suggesting this may be an underestimate.
Number of patients with ATTRm genotype	Year 1: 200 Year 6: 216	Expert opinion	Initial estimate of 200 patients (representing 6.8% of ATTR-CM population) inflated annually by ABS population growth. The estimate is substantially lower than the proportion of ATTRm patients enrolled in the ATTR-ACT trial (ATTRm 24%), and the commentary considered it was likely to be an underestimate.
Proportions of patients suspected to have ATTR-CM	Year 1: 76% Year 6: 84%	Physician survey conducted for the submission.	The survey included 37 cardiologists with 3-30 years of practice, who have suspected or confirmed a diagnosis of ATTR-CM within the prior two years. Physicians reported varying involvement in diagnosis and ongoing management. The commentary considered that it was unclear whether the proportion of patients with suspected ATTR-CM included patients with HFpEF or amyloid deposition, and may have included patients referred by GPs and other cardiologists. The commentary considered that the reported proportions of patients suspected, tested, diagnosed and likely to be treated with tafamidis may include duplicated data from individual patients referred between responding physicians.
Proportion of patients tested for ATTR-CM	Year 1: 89% Year 6: 98%		
Proportion of patients diagnosed with ATTR-CM	64%		
Proportion of patients treated for ATTR-CM	Year 1: 46% Year 6: 79%		
Proportion of patients treated with tafamidis	Year 1: 58% Year 6: 72%		
Utilisation model			
Probability of survival	-	All-cause mortality from ATTR-ACT and extension study, extrapolated over 6 years using the gamma function	
Probability of treatment discontinuation	-	Treatment discontinuation from ATTR-ACT, extrapolated over 6 years using the lognormal function	
Costs of MBS items used for diagnosis of ATTR-CM			
Average cost of local or whole body bone scans	\$480.83	Average of cost of MBS items 61446, 61449, 61421, 61425, 61425 and 61505	The MBS items selected for inclusion were not adequately justified. The MSAC considered that new services associated with use of tafamidis are able to be performed under existing MBS items 61446 and 61449 for localised bone study. Inclusion of whole body scan items may overestimate the cost of additional services (MSAC Public Summary Document 1584, 76th MSAC meeting 1-2 August 2019). The costs of MBS services are inappropriately included at 100% of the scheduled fee.

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Data	Value	Source	Comment
Proportion of eligible patients receiving bone scans	90%	Expert opinion.	The commentary considered this may be reasonable.
Myocardial biopsy, by cardiac catheterisation (item 38275)	\$302.95	MBS item 38275	The commentary considered this was reasonable. However, the costs of MBS services are inappropriately included at 100% of the scheduled fee.
Cost of other tissue biopsies	0	Assumed.	The commentary considered this may be reasonable. However, additional MBS costs may accrue for review of biopsies.
Proportion of eligible patients receiving biopsies	Myocardial - 10% Other - 10%	Expert opinion.	Assumed.

Source: Table 4.1.1, p.214, Section 4.1, pp.214-215, and Utilisation-and-cost-model-tafamidis_final.xlsx, of or attached to the submission. Abbreviations: ABS, Australian Bureau of Statistics; ATTR-CM, cardiac transthyretin amyloidosis; ATTRm, variant (mutated) transthyretin amyloidosis; ATTRwt, wild type transthyretin amyloidosis; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NA, not applicable; yrs, years.

6.69 The table below presents the estimated use and financial impact of listing tafamidis on the PBS.

Table 18: Estimated use and financial implications of listing tafamidis on the PBS (est. 2021-2026)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated utilisation of tafamidis						
Prevalent population with ATTR-CM	█	█	█	█	█	█
Incident patients treated with tafamidis	█	█	█	█	█	█
All patients treated with tafamidis (incident+prevalent)	█	█	█	█	█	█
Average scripts per year ^a	█	█	█	█	█	█
Number of scripts per year	█	█	█	█	█	█
Estimated financial implications of tafamidis to the PBS/RPBS (effective price)						
Cost of tafamidis to PBS/RPBS less copayment	\$█	\$█	\$█	\$█	\$█	\$█
Net financial implications of tafamidis (effective price)						
Net cost to PBS/RPBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to MBS	\$█	\$█	\$█	\$█	\$█	\$█
Net cost to PBS/RPBS/MBS	\$█	\$█	\$█	\$█	\$█	\$█

Source: Tables 4.1.2, p.216, 4.2.1 and 4.2.2, p.218, 4.2.3, pp.220-223, 4.2.4 and 4.2.5, p.224, 4.2.7, p.225 and 4.2.8, p.226 of the submission; Utilisation-and-cost-model-tafamidis_final.xlsx, attached to the submission.

Abbreviations: ATTR-CM, cardiac transthyretin amyloidosis.

^a Based on the number of patients alive and on treatment each month, assuming 1 script per patient per month. Given a script provides 30 days of tafamidis, it would be more appropriate to assume 1.014 [365/30/12] scripts per patient per month.

The redacted table shows that at Year 6, the estimated number of scripts was 10,000 – 50,000.

6.70 The submission estimated that the net cost to the PBS/RPBS of tafamidis (effective price) was \$20 - \$30 million in Year 1, increasing to more than \$100 million in Year 6, a total of more than \$100 million over 6 years. The net impact to the PBS/RPBS and the MBS was estimated to be more than \$100 million over 6 years.

- 6.71 The submission estimated that approximately less than 10,000 patients currently treated with tafamidis in compassionate programs or clinical studies would require grandfather treatment. DUSC considered that the submission's approach to including grandfather patients (distributing incident patients in Year 1, divided evenly throughout the year over monthly cycles) would underestimate the financial impact of these patients.
- 6.72 DUSC considered the estimated net cost of tafamidis was significantly underestimated due to the following issues:
- The estimated eligible Australian population likely to be treated with tafamidis was based on the product of multiple factors (estimated proportions of patients with preserved ejection fraction, amyloid deposition, likely to be suspected, likely to be tested, likely to be diagnosed, likely to be treated, likely to be treated with tafamidis), and upscaling adjustments (proportions female, ATTR_m, reduced ejection fraction), based on data sources with various issues (underestimates compared with alternative sources, use of older data not applicable to current Australian clinical practice, unsupported assumptions), resulting in substantial cumulative uncertainty, and overlap between factors. For example:
 - DUSC noted that the source used to estimate the prevalence of females with ATTR_{wt}, and ATTR_m related ATTR-CM could not be located, but the estimate (6%) was lower than reported in the ATTR-ACT trial (9.7%) and the published literature (up to 19%, Gonzales-Lopez et al. 2017). DUSC considered that the sponsor's female estimate was most likely underestimated.
 - The estimated proportions of males aged ≥ 60 years with heart failure were based on self-reported cases collated in the ABS Australian Health Survey 2011-2012, excluding patients in hospitals, and nursing or convalescent homes, and are most likely underestimated. More recent clinical studies of the prevalence of heart failure in the Australian setting have estimated a higher prevalence (Chan et al. 2015; Abhayaratna et al. 2006).
 - The decreasing numbers of prevalent patients over the six year estimates, and decreasing numbers of incident patients after Year 2 do not meet face validity given the increase in the prevalence of heart failure in the Australian setting over time (Heart Foundation, Australia; Chan et al. 2015). The PSCR argued that the estimates of HFrEF patients reduced over time due to likely earlier identification and slowing of progress to reduced ejection fraction based on advice from clinical experts. Due to the decreasing number of these patients, the number of prevalent patients appears to decrease over time. DUSC did not agree with the PSCR and considered that the resulting decreasing prevalent population modelled over the six year period does not meet face validity.
 - DUSC considered that the estimated prevalence of patients with heart failure with preserved ejection fraction, based on 30 year old US data from one Midwestern county, is unlikely to reflect prevalence in the current Australian setting, and is most likely a substantial underestimate.

- The estimated prevalence rates of amyloid deposition in patients with heart failure with preserved ejection fraction were based on incidental findings in patients aged 75 years and older (Mohamed-Salem et al. 2018). DUSC considered these estimates are unlikely to be representative of amyloid disposition in the target population. It is unclear how amyloid deposition in younger patients aged < 75 years were determined for the submission.
- The submission assumed that the prevalence of eligible patients with heart failure with reduced ejection fraction would decrease over time due to treatment with tafamidis. This assumption was not adequately supported by the clinical data, and may not reflect the ATTR-CM disease trajectory in the Australian setting if tafamidis is listed on the PBS. In addition, the proportions of patients with preserved ejection fraction was not adjusted for the estimated reduction in heart failure progression.
- DUSC considered the submission's approach to deriving the incident population, distributing each year's population over monthly cycles was overly complex and may include double counting of prevalent patients and inadequately accounting for grandfathered patients underestimates the financial implications.

Quality Use of Medicines

- 6.73 The sponsor stated that it had established an education steering committee including an amyloid specialist, nuclear physicians and cardiologists, to develop a training program for clinicians to increase disease awareness and facilitate earlier diagnosis.
- 6.74 DUSC noted that the submission had not outlined the possibility of drug-drug interactions despite the only clinical trial (ATTR-ACT) excluding people receiving calcium channel blockers or digoxin. The pre-PBAC response stated that these medicines are contraindicated as they bind to amyloid fibrils and may increase toxicity and hence excluded from the trial. The pre-PBAC response provided no further information on the estimated number of patients currently using these two therapies who may be impacted.

Financial Management – Risk Sharing Arrangements

- 6.75 The submission acknowledged the uncertainty around the utilisation and financial implications to the PBS of listing tafamidis, and suggested a volume-based risk sharing arrangement (RSA) may be appropriate. Details of a proposed RSA were not included in the submission or the PSCR. The limitations of the data and methodology that make it difficult to estimate the eligible population size would also make it difficult to establish an appropriate volume cap for the target ATTR-CM population.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC did not recommend tafamidis for the treatment of patients with transthyretin amyloid cardiomyopathy (ATTR-CM). The PBAC accepted that tafamidis

was clinically superior to current standard management. However, the PBAC considered that the incremental cost-effectiveness ratio (ICER) had not been reliably estimated and was unacceptably high at the price proposed in the submission. The PBAC considered that the financial estimates were highly uncertain and highly likely to be underestimated.

- 7.2 The PBAC considered there is a high unmet clinical need for effective therapies for ATTR-CM. The PBAC acknowledged the consumer comments in support of listing tafamidis, which described the fear of disease progression given the poor prognosis, the significant impact that symptoms (e.g. shortness of breath and fatigue) have on a patient's quality of life, and the lack of effective therapies to treat this condition.
- 7.3 The PBAC agreed with the ESC that the restriction should more closely align with the ATTR-ACT trial inclusion and exclusion criteria with regard to: requiring evidence or history of heart failure; requiring patients to have NYHA Class I to III; requiring patients to have an end-diastolic interventricular septal wall thickness ≥ 12 mm; and excluding patients with eGFR $< 25\text{mL}/\text{min}/1.73\text{m}^2$. The PBAC considered that patients should discontinue tafamidis if they progress to NYHA Class IV, or receive a heart or liver transplant or an implanted cardiac ventricular assist device.
- 7.4 While the trial required endomyocardial biopsy to confirm the diagnosis of ATTR-CM, the submission proposed the use of bone scintigraphy (in combination with screening for monoclonal protein and, in specific cases, histological confirmation). MSAC advised the PBAC that the diagnostic performance of cardiac scintigraphy via bone studies should be considered acceptably similar to endomyocardial biopsy for the purposes of determining eligibility for tafamidis. The PBAC noted that the data supporting the use of bone scintigraphy (Gillmore et al 2016) were based on use in a specialised amyloid centre, and considered that the positive predictive value may not be reproduced in non-specialised centres given that interpretation of bone scans is potentially subjective. The PBAC considered that data regarding the positive predicted value of bone scintigraphy in non-specialised centres (as part of the diagnostic algorithm proposed by the submission) would be informative.
- 7.5 The PBAC noted that the proposed use of bone scintigraphy in this clinical area is evolving, and considered that a uniform approach would help achieve reliable and consistent diagnostic practices (e.g. with guidelines supporting the new algorithm) when determining eligibility for tafamidis. The PBAC was concerned about the potential for inconsistency in bone scintigraphic reporting, especially by facilities with little prior experience or expertise in reporting studies for the diagnosis of ATTR-CM.
- 7.6 The PBAC considered that the proposed new diagnostic algorithm (along with the availability of an effective therapy) will lead to changes in testing practices over time, likely identifying previously undiagnosed patients or patients at earlier stages of disease, and with significant potential effects on the number of eligible patients and on the baseline risk of the overall eligible population. Further, the PBAC considered this will likely have significant effects on utilisation of MBS-funded bone scintigraphy.

The PBAC agreed with the ESC that some of these newly diagnosed patients may have more benign clinical courses and that the overall natural history of ATTR-CM may evolve with changing diagnostic paradigms.

- 7.7 The PBAC considered that standard management was the appropriate comparator.
- 7.8 The PBAC accepted the claim of superior efficacy compared with standard management. The submission was based on the ATTR-ACT trial, which was a randomised placebo controlled trial comparing tafamidis in combination with standard management to standard management alone. The primary outcome was a Finkelstein-Schoenfeld prioritised pairwise comparison of all-cause mortality and cardiovascular hospitalisations versus placebo (p-value = 0.0006 for the tafamidis pooled arm). The two component outcomes were also statistically significantly in favour of tafamidis (pooled arm) with a Cox-proportional hazard ratio (HR) for all-cause mortality of 0.70 (95% CI: 0.51, 0.96) and a relative risk for cardiovascular hospitalisations of 0.68 (95% CI: 0.56, 0.81). The PBAC noted the observed treatment effect of tafamidis on all-cause mortality emerged after approximately 18 months of treatment.
- 7.9 The PBAC considered that the magnitude of benefit in the Australian PBS population was uncertain due to:
- Subgroup data from the ATTR-ACT trial suggest that NYHA Class may be a treatment effect modifier, with tafamidis treatment being associated with an increase in hospitalisations and an uncertain impact on survival in patients with NYHA Class III disease. The PBAC considered that the increased rate of hospitalisations in patients with NYHA Class III treated with tafamidis compared to placebo was not adequately explained, and was a significant concern because a large proportion of patients in clinical practice will be NYHA Class III (the submission estimated that 37% of patients treated with tafamidis would have NYHA Class III).
 - It was unclear whether the distribution of NYHA classes from the ATTR-ACT trial will be applicable to the Australian setting, particularly as changes in the diagnostic algorithm will likely affect the distribution of NYHA classes among patients with ATTR-CM and hence the overall benefit and cost-effectiveness of tafamidis. The pre-PBAC response argued that earlier diagnosis will better align the PBS population with those in ATTR-ACT (including in terms of distribution by NYHA class) and that treating a higher proportion of patients with NYHA Class II disease will be more cost-effective. However, the PBAC considered that it was unclear whether newly diagnosed patients would have more benign clinical courses and that the overall natural history of ATTR-CM may evolve with changing diagnostic paradigms.
 - The PBAC noted that the baseline risk of death varies substantially between NYHA classes and TTR genotypes, and thus the absolute benefit of tafamidis treatment in the likely Australian PBS population was uncertain.

- 7.10 The PBAC noted that results for key outcomes were similar for the 20 mg and 80 mg doses of tafamidis. For example, the proportion of patients alive at 30 months was similar between the tafamidis treatment arms (72.7% and 69.3% for the 20 mg and 80 mg arms, respectively versus 57.1% for placebo), however the sponsor had not sought registration or listing of the 20 mg once daily dose. The PBAC considered that adequate justification for the 80 mg dose rather than the 20 mg had not been provided.
- 7.11 The PBAC considered that the claim of non-inferior safety versus standard management was possibly reasonable, noting there were no significant toxicity or safety signals with tafamidis in the trial. However, the PBAC considered that the clinical safety dataset was small and inadequate to make a claim of non-inferior safety.
- 7.12 The PBAC agreed with ESC that the structure of the economic model did not form a reliable basis for decision marking as:
- the model assumed patients remain in the same NYHA class over the duration of the model, which the ESC and PBAC considered was inappropriate as it did not capture the progressive nature of ATTR-CM;
 - a constant probability of hospitalisation was applied over the duration of the model, which was inappropriate as cardiovascular hospitalisations would generally be expected to increase with age;
 - the implicit assumption that all cardiovascular hospitalisations were non-fatal was inappropriate as the cardiovascular hospitalisation rates reported in the ATTR-ACT trial included fatal and non-fatal events; and
 - the implicit assumption that the estimated treatment effect is maintained following treatment discontinuation was inappropriate as increasing proportions of patients discontinue over time and spend longer durations without therapy (where they do not accrue drug costs but do derive treatment benefit).
- 7.13 The submission applied different parametric functions to the tafamidis and best supportive care arms. The PBAC agreed with the ESC that it would be more appropriate to apply the same function to both arms given the differences in model fit were small and the proportional hazards assumption between treatments did not appear to be violated. Further, the PBAC noted that nearly all of the benefits occurred during the extrapolated part of the model (96% the incremental life years occurred beyond 30 months), and considered that this further increases the uncertainty of the model estimates.
- 7.14 The PBAC considered that there were substantial differences in modelled incremental benefits associated with tafamidis treatment in patients with NYHA Class I/II and those with NYHA Class III heart failure. The PBAC agreed with the ESC that it is unclear whether the distribution of NYHA classes from the ATTR-ACT trial would be applicable

to the Australian setting, e.g. the distribution is likely to be affected by any changes in practices around testing for ATTR-CM.

- 7.15 Overall, the PBAC agreed with the ESC that the submission's estimate of cost-effectiveness was unreliable given the major structural limitations of the model and the uncertain proportion of patients across NYHA classes. Notwithstanding this, the PBAC noted that the submission had estimated an ICER of more than \$200,000 per QALY gained. The PBAC considered this ICER was unacceptably high, and that a significantly lower and more certain ICER would be required.
- 7.16 The PBAC agreed with DUSC and considered that the submission had likely substantially underestimated the financial implications, as outlined in Paragraph 6.71. Key issues included:
- ATTR-CM is likely currently significantly underdiagnosed but this is difficult to quantify due to the nature of the data sources available. Changes in the diagnostic algorithm, along with the availability of an effective treatment for this condition will likely increase patient numbers.
 - The prevalent population was highly uncertain and likely to have been significantly underestimated: (1) The population with heart failure was based on self-reported data which was likely to be under-reported; (2) The estimated prevalence of patients with heart failure with preserved ejection fraction was likely underestimated as it was based on data from 30 years ago; and (3) Amyloid deposition rates were age-stratified and based on screening of 31 asymptomatic patients 75 years and older. Rates for younger patients were based on linear extrapolations but there does not appear to be a linear association between amyloid deposition rates with age.
 - The PBAC considered that the decreasing prevalent and incident populations do not meet face validity given the increase in the prevalence of heart failure in the Australian setting over time.
 - As outlined in Paragraph 7.6, the PBAC considered that the proposed new diagnostic algorithm will lead to changes in testing practices over time and the impact of these changes to the MBS was likely to have been significantly underestimated.
- 7.17 Given the significant issues with estimating the eligible population and the very high financial impact, the PBAC considered that further work was required to determine the size of the eligible population in Australia, particularly the incidence and prevalence of the condition.
- 7.18 The PBAC considered that more reliable financial estimates would be required to inform a RSA.
- 7.19 The PBAC considered that any resubmission would need to be a major submission and should include the following:
- the requested listing should be revised as outlined above and in Section 3;

- further information regarding the efficacy of tafamidis in patients with NYHA Class III would be required to address the PBAC’s concerns regarding the increased rate of hospitalisations in this subgroup;
- address the issues with the economic model outlined above and as identified by ESC in the ‘Economic analysis’ section. The PBAC considered that a significantly lower and more certain ICER would be required for tafamidis to be considered suitably cost-effective;
- address the issues with the financial estimate outlined above and as identified by DUSC. The PBAC considered that greater certainty would be required around the financial estimates, particularly the prevalence and incidence rates; and
- an RSA which adequately addresses the uncertainties with the use of tafamidis in a broad population.

7.20 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor’s Comment

Pfizer welcomes the PBAC’s acknowledgement of the high unmet clinical need for effective therapies for ATTR-CM and acceptance of the superiority of tafamidis over standard management. Pfizer will continue to work collaboratively with the PBAC to deliver access to tafamidis for patients with this debilitating and life-threatening condition.