7.07 TAFAMIDIS, Capsule 61 mg, Vyndamax®, Pfizer Australia Pty Ltd.

1 Purpose of submission

1.1 The Standard Re-entry submission requested an Authority Required listing for tafamidis for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) in patients with NYHA class I-II heart failure and an end-diastolic interventricular septal wall thickness of at least 12 mm. The PBAC has previously considered tafamidis for ATTR-CM at its July 2020, March 2021 and September 2021 meetings.

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard management of ATTR-CM.

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

Component	Description
Population	Wild-type or variant transthyretin cardiac amyloidosis in patients with NYHA class I-II. Patients who transition to NYHA class III (confirmed by a further assessment after 3-6 months) or NYHA class IV, are to be discontinued.
Intervention	Tafamidis 61 mg capsules taken once daily (bioequivalent to tafamidis meglumine 80 mg)
Comparator	Standard ATTR-CM management (e.g. diuretics and anti-arrhythmics)
Outcomes	All-cause mortality, frequency of cardiovascular-related hospitalisations, change in the distance walked during 6MWT, change in quality of life scores (KCCQ – OS, EQ-5D-3L), cardiovascular-related mortality, TTR stabilisation at Month 1.
Clinical claim	Tafamidis has superior efficacy and inferior safety compared to standard ATTR-CM management.

Source: Table 1.1.1, p4 of the resubmission; Section 2.8, p212 of the resubmission. Changes from the March 2021 submission underlined.
Abbreviations: 6MWT, six-minute walk test; ATTR-CM, cardiac transthyretin amyloidosis; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; TTR, transthyretin.

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 the tafamidis meglumine 80 mg formulation (four 20 mg capsules), used in the key clinical trial (TGA Clinical Evaluation Report: Round 2).

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).

Previous PBAC consideration

2.4 An Early Resolution submission was considered by the PBAC at the September 2021 PBAC meeting. However, tafamidis was not recommended for the treatment of patients with ATTR-CM as changes made in the resubmission did not sufficiently address the Committee's previous advice and did not meet the criteria for early resolution (i.e. required evaluation).

2.5 Table 2 summarises the key matters of concern from the September 2021 early resolution resubmission.

Table 2: Summary of key matters of concern

Matter of concern	Addressed in the resubmission
Economic evaluation	
In March 2021 the PBAC considered the outstanding economic issues may be addressed in a simple resubmission if the following changes were made, without any additional amendments to the economic evaluation: an ICER of $80,000/QALY gained for the model, applying the 2 sensitivity analyses in the pre-PBAC response (allowing for increasing mortality over time, and a reduced treatment effect for tafamidis on mortality to account for treatment-related discontinuation), and correcting for errors in the calculation of acute disease costs and disease management costs, and the inappropriate use of MBS benefit rather than MBS fee as per the evaluation (para 9.1). The PBAC considered that the changes made in the September 2021 resubmission did not sufficiently address the Committee's previous advice regarding the requirements of a simple resubmission. In particular, the PBAC considered that the ICER stated in the resubmission ($[redacted][1]/QALY gained) was significantly higher than the ICER requested ($80,000/QALY gained) and noted that it relied on tafamidis being discontinued in patients with persistent class III heart failure (para 10.1). This change was not requested by the PBAC and resulted in significant changes to the economic model (para 9.3). At the September 2021 meeting, the PBAC reiterated that a resubmission for tafamidis should address the following issues which remain outstanding from the March 2021 PSD: An ICER of $80,000/QALY gained for the model applying the two sensitivity analyses in the pre-PBAC response (para 10.4).	The economic analysis presented in the current resubmission is largely unchanged from the September 2021 model. The model corrected the errors in costs identified in the March 2021 evaluation and incorporated the changes that were presented in the 2 sensitivity analyses presented in the March 2021 pre-PBAC response. However, the model also incorporated discontinuation of patients with persistent NYHA class III heart failure, which was not requested by the PBAC, and which the PBAC considered would be difficult to implement in practice. An error in the application of this change increased the ICER to $[redacted][1] per QALY gained (compared to the resubmission's base case of $[redacted][2] per QALY gained). The resubmission stated that the sponsor is unable to meet the $80,000 ICER, but reductions in the published and effective prices for tafamidis were proposed in the resubmission (an effective DPMQ of $[redacted] for the first 3 years and $[redacted] for subsequent years; compared with $[redacted] for the first 3 years and $[redacted] for subsequent years in the September 2021 submission; $[redacted] in the March 2021 submission; and $[redacted] in the July 2020 submission).
Utilisation and financial impact of listing	
The PBAC considered that the resubmission's proposal for tafamidis to be discontinued in patients with persistent class III heart failure may be difficult to implement in practice given the subjective nature of NYHA classification and would likely result in use outside the restriction (para 10.2). Notwithstanding this, the PBAC considered that this patient population (i.e. patient numbers derived based on patients with NYHA class I, II and non-persistent class III heart failure) may form a reasonable basis for the risk sharing arrangement (RSA) expenditure caps, given the Committee previously considered that the efficacy was uncertain in patients with NYHA class III	The resubmission proposed a special pricing arrangement (see above). The resubmission assumed that patients progressing from NYHA class I-II heart failure will be identified in the Australian setting, and estimated the utilisation and cost of tafamidis use in the narrower eligible Australian excluding patients with persistent NYHA class III or NYHA class IV heart failure. The resubmission used the proportions of transitions between NYHA classes observed in the ATTR-ACT trial at 6 month intervals to estimate transitions in the Australian setting.

Matter of concern	Addressed in the resubmission
heart failure (para 7.7, Tafamidis PSD, March 2021 PBAC meeting) (para 10.3). The PBAC considered that the total financial expenditure remained high and the proposed RSA, with expenditure caps higher than the resubmission's estimated financial expenditure, would not adequately manage the risk associated with use in a broader population in which cost-effectiveness is unknown (para 10.1). The PBAC reiterated that a resubmission for tafamidis should address the following issues which remain outstanding from the March 2021 PSD: outline an RSA to provide more certainty with respect to the total cost, and to manage the risk associated with use in a broader population in which cost-effectiveness is unknown (para 10.4).	In addition, the resubmission proposed a risk sharing arrangement to address the uncertainty, with caps set at 100% of estimated expenditure with [redacted]% rebate in Years 1-3 of listing and at 105% of estimated expenditure with a [redacted]% rebate in Years 4-6 of listing.

Source: Tafamidis PSD and PBAC PSD, March 2021 PBAC meeting with September 2021 Addendum; and Overview, ppxv-xix of the resubmission.
Abbreviations: DPMQ, dispensed price for maximum quantity; NYHA, New York Heart Association; PBAC, Pharmaceutical Benefits Advisory Committee; PSD, Public Summary Document; RSA, risk sharing arrangement.
The redacted values correspond to the following ranges:
[1] $135,000 to < $155,000
[2] $95,000 to < $115,000

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

3 Requested listing

3.1 The requested restriction, shown below, was unchanged from the September 2021 resubmission.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
TAFAMIDIS					
Tafamidis 61 mg tablet (30)	$[redacted] (published) $[redacted] (effective; Years 1-3) $[redacted] (effective; Years 4-6)	1	30	5	Vyndamax

Category / Program: General Schedule (GE)
Prescriber type: ☒Medical Practitioners
Treatment Phase: Initial treatment phase
Restriction type: ☒Authority Required (in writing only via post/HPOS upload)
Indication: Transthyretin amyloid cardiomyopathy
Clinical criteria:
The condition must be wild type transthyretin amyloidosis; or the condition must be variant transthyretin type amyloidosis
AND
Clinical criteria:
Patient must have evidence or history of heart failure
AND
Clinical criteria:
Patient must have New York Heart Association class I to II heart failure.
AND
Clinical criteria:

The condition must have an end-diastolic interventricular septal wall thickness of at least 12 mm.
AND
Clinical criteria:
The condition must have the presence of transthyretin precursor protein as identified by one of the following: (i) Histological confirmation with either immunohistochemistry (confirmed by amyloid expert centre) or mass spectrometry; or (ii) 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.
AND
Clinical criteria:
Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 mL/min/1.73 m^2.
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.
Prescribing Instructions: Evidence or history of heart failure must comprise one of the following: (i) History of one or more hospitalisations for heart failure, (ii) Clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement.
Treatment Phase: Continuing treatment phase
Restriction type: ☒Authority Required – immediate/real time assessment by Medicare (telephone/online/emergency)
Indication: Transthyretin amyloid cardiomyopathy
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
AND
Clinical criteria:
Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 mL/min/1.73 m^2.
AND
Clinical criteria:
Patient must have New York Heart Association class I to II 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.
Prescribing Instructions:
The treatment must be ceased if any of the following occur: (i) Patient progresses to New York Heart Association class III confirmed by a further assessment within 3-6 months. (ii) Patient progresses to New York Heart Association class IV heart failure. (iii) Patient receives a heart / liver transplant, or an implanted cardiac ventricular assist device.

Source: Tables 1.4.2 and 1.4.3, pp36-37 of the resubmission.

3.2 The resubmission proposed a special pricing arrangement with an initial effective price of $ (DPMQ) for Years 1 to 3 of listing, and $ (DPMQ) for Years 4 to 6 of listing. This was lower than the proposed price in the March 2021 resubmission ($ DPMQ), and the proposed price in the September 2021 resubmission ($ DPMQ for Years 1 to 3; $ DPMQ for Years 4 to 6). The pre-PBAC response proposed a revised effective price from the 4th year of listing from $ to $ DPMQ and a reduction in the published price from $ to $.

3.3 The requested restriction is narrower than the registered TGA indication, as it limits eligibility for initiation of PBS listed tafamidis to patients with NYHA class I to II heart failure with an end-diastolic interventricular septal wall thickness ≥ 12 mm, and eGFR >25mL/min/1.73m^2. Patients who progress to persistent NYHA class III heart failure or NYHA class IV heart failure may not continue PBS subsidised treatment.

3.4 At the September 2021 meeting, the PBAC considered that the proposal for tafamidis to be discontinued in patients with persistent NYHA class III heart failure may be difficult to implement in practice given the subjective nature of the NYHA classification, and would likely result in use outside the restriction (para 10.2, Tafamidis Public Summary Document (PSD), March 2021 PBAC meeting with September 2021 addendum). The resubmission stated that the implementation of this restriction has been discussed with clinical experts who confirmed that discontinuation of tafamidis in patients with NYHA class III heart failure could be managed in clinical practice. The ESC reaffirmed that this would likely lead to use outside of the restriction in patients commenced on tafamidis who had progressed, but where the patient and the clinician were unwilling to stop the medication in case tafamidis was slowing progression. The PBAC considered the wording of this criterion could be further refined and clarified. The PBAC considered that review of patients progressing to NYHA class III after 3 months would allow sufficient time to restabilise the patients with diuretics and dose adjustments of other medications.

3.5 Consistent with the previous submissions, the resubmission did not specify what documentation, if any, would be required to be provided as part of the initial written Authority application. The PBAC agreed with ESC that it would be preferable for the initial written authority application to require confirmation that there is evidence of heart failure (echocardiogram or magnetic resonance imaging), and confirmation that there is evidence of ATTR (bone scintigraphy and pathology results, or histological confirmation).

3.6 A grandfather restriction was not proposed. The resubmission estimated that approximately 300 patients may be grandfathered onto PBS subsidised tafamidis. The PBAC considered a separate grandfather restriction is not required as these patients would be eligible to access treatment under the initial treatment restriction.

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

4 Population and disease

4.1 Transthyretin amyloidosis (ATTR) is a rare systemic disorder caused by the extracellular deposition of misfolded transthyretin (TTR) amyloid fibrils in affected organs and tissues. ATTR can be inherited as an autosomal dominant variant of the TTR gene (ATTRv; also referred to as hereditary ATTR, or hATTR) or caused by the deposition of wild-type transthyretin protein (ATTRwt). The TTR amyloid protein can infiltrate many vital organs and tissues, but most affected patients present with one

of two predominant phenotypes: ATTR related cardiomyopathy (ATTR-CM), or ATTR related polyneuropathy (ATTR-PN) (Kittleson et al. 2020).

4.2 ATTR-CM is a rare, late onset, progressive disease, characterised by ATTR fibril deposition in the cardiac atrial and ventricular walls, and/or direct amyloid proteotoxicity (Siddiqi et al. 2018; Kittleson et al. 2020). ATTR fibril deposition results in progressive myocardial hypertrophy, restrictive cardiomyopathy with diastolic dysfunction (with or without systolic dysfunction), and progressive fulminant 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), or atrioventricular conduction defects (e.g. heart block; bundle branch block).

4.3 ATTR-CM is related to either the ATTRwt or ATTRv genotypes, and is most prevalent in males ≥ 60 years of age, with prevalence increasing with age (Siddiqi et al. 2018). Median age at diagnosis has been estimated at 75 years (range 47-94 years; Grogan et al. 2016). However, age of onset, presentation and prognosis vary between TTR genotypes and ATTRv mutations. Cardiac amyloidosis is the dominant feature of the ATTRwt genotype. ATTRv cardiomyopathy varies in prevalence and pattern of organ involvement by mutation, and may involve a combination of amyloid polyneuropathy and cardiomyopathy.

4.4 ATTR-CM commonly presents with systemic manifestations of fibril deposition; e.g. carpal tunnel syndrome, lumbar spinal stenosis, bicep tendon rupture, bilateral ascending sensory-motor polyneuropathy, dysautonomia, diarrhoea/constipation, erectile dysfunction, and glaucoma (Siddiqi et al. 2018). However, diagnosis of ATTR-CM is difficult and 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 ATTRv and 3.5 years for ATTRwt, with death most likely due to cardiovascular causes (cardiac arrhythmia, fulminant heart failure; Dungu et al. 2012; Maurer et al. 2017; Ruberg et al. 2012).

4.5 The current and proposed clinical management algorithms in the submission were the same as presented in the March 2021 and September 2021 submissions, with standard management of ATTR-CM related heart failure (i.e. symptomatic treatment with appropriate diuretics and antiarrhythmics), as a treatment option prior to or concomitant with tafamidis. This positions tafamidis as a disease modifying treatment in addition to or in place of standard management of ATTR-CM heart failure, in patients with ATTR-CM related heart failure, confirmed by bone scintigraphy with histological confirmation of transthyretin precursor protein in cardiac tissue, and immunochemistry or mass spectrometry as required, with or without gene testing. The Pre-Sub-Committee Response (PSCR) provided a revised current clinical algorithm including updated diagnosis procedures (scintigraphy +/- histological confirmation, as in the proposed treatment algorithm) which the PSCR noted have become the standard diagnostic method. The submission and PSCR claimed that diagnosis of ATTR-CM has increased since the previous submission due to the availability of a non-invasive diagnostic method and will further increase with the listing of tafamidis.

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

5 Comparator

5.1 The resubmission nominated standard management of the symptoms of ATTR-CM heart failure as the main comparator. The PBAC previously considered that standard management of ATTR-CM is the appropriate comparator (para 7.7, Tafamidis PSD, July 2020 PBAC meeting; para 7.3, Tafamidis PSD, March 2021 PBAC meeting).

5.2 Patisiran for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy will also be considered by the PBAC at the July 2023 meeting (item 5.09 refers). The ESC noted the PSCR questioned the relevance of the comparison between tafamidis and patisiran. However, the ESC considered that there would potentially be some overlap in the proposed populations eligible for tafamidis and patisiran despite the different manifestations of ATTR amyloidosis targeted by the two submissions.

5.3 Top line results of the patisiran ATTR-CM APOLLO-B trial (n=360) showed statistically significant benefits to patients with cardiomyopathy at 12 months in terms of functional capacity (6MWT) and health status/quality of life (KCCQ-OS) compared to placebo, but no statistically significant benefits in terms of all-cause mortality and key composite outcomes comprised of mortality, frequency of cardiovascular events, hospitalisations, and urgent heart failure related hospitalisations (Maurer et al. 2022).

5.4 In addition, an open-label study of inotersen suggested some efficacy in the treatment of ATTR-CM (Dasgupta et al. 2020).

5.5 Given inotersen and patisiran are not registered for the treatment of ATTR-CM in Australia and the current clinical evidence for both agents for this indication is limited, neither agent was nominated as a potential near market comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician discussed the course of symptoms, diagnosis and current treatments for ATTR-CM. The clinician noted that genetic testing can sometimes identify a rare form of the condition and allow patients to access clinical trials for new treatments. Most patients (90%) are wild type for the ATTR gene and those with the ATTR gene tend to be younger. The clinician noted that tafamidis is the only TGA approved drug for this indication and has good evidence of stabilising disease and improved or prolonged quality of life. The clinician noted that there is increased awareness of ATTR, especially in heart failure with preserved ejection fraction but rates of referral and diagnosis are still low. The clinician considered that patients can revert from NYHA Class III or IV back to Class II and noted

that the stopping rule proposed should be explained to patients prior to initiating tafamidis. The PBAC considered that the hearing was moderately informative as it provided a clinical perspective on managing the proposed stopping rule.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (26), and organisations (2) via the Consumer Comments facility on the PBS website. The comments from patients treated with tafamidis described the benefits of treatment in terms of stabilisation of amyloid deposits in the heart. Input from individuals with ATTR-CM described its impact on quality of life, particularly on fatigue and weakness, with comments noting improvements observed due to tafamidis treatment, including stabilisation of quality of life and the ability to return to work and exercise. Individuals who would like to access tafamidis described the hope that it will improve functional capacity, symptoms of peripheral neuropathy and autonomic nervous system symptoms, improve quality of life and even extend life. Input from individuals also outlined the prohibitive cost of tafamidis and noted the preference for oral administration. Comments described side effects as minor and more tolerable than other treatments used for management of symptoms. The PBAC noted that consumer comments for the previous tafamidis submissions reflected similar views.

6.3 The PBAC noted advice received from Amyloidosis Research Consortium (ARC), which provided results of a global survey of 390 ATTR patients (41% with CM only and 40% with both CM and PN). The most common symptoms reported for ATTR-CM patients were fatigue (87%), shortness of breath (77%), and muscle weakness or loss of strength (71%). The symptoms impacting ATTR-CM patients most significantly were sexual dysfunction (47%), fatigue (46%) and pain, numbness, or tingling in feet/legs (41%). In terms of mental/emotional impacts the most commonly reported significant impact was worry about the future (29%), worry that they may not be able to access the treatments that they need for ATTR (19%) and fear or anxiety related to ATTR (21%).

6.4 The PBAC noted input from the Australian Amyloidosis Network (AAN), describing diagnosis of ATTR-CM and the treatment benefit and tolerability of tafamidis. Input from AAN stated that there is now consensus that ATTR-CM can be accurately diagnosed without the need for cardiac biopsy by the use of bone scintigraphy, and that the quality of bone scintigraphy reports for cardiac amyloidosis has improved significantly with greater use of SPECT imaging, appropriate scan timing and more uniform reporting. AAN also noted that around 20% of patients with positive cardiac bone scintigraphy require demonstration of amyloid on a tissue biopsy with subtyping by immunohistochemistry or mass spectrometry in order to distinguish AL from ATTR amyloidosis. Immunohistochemistry to diagnose amyloid subtype is highly specialized and technically difficult and the AAN recommended that it be performed only in specialized amyloidosis centres, and consideration of greater resourcing for these services may be required.

Clinical trials

6.5 The current resubmission relied on the same clinical trial data previously considered by the PBAC. The key differences between the March and September 2021 resubmissions, and the current resubmission are as follows:

- Updated long term follow-up data from the ATTR-ACT trial extension study, B3461045.
- New supporting evidence from 11 nonrandomised studies.
- Updated Periodic Safety Update Report and extended assessment of comparative harms.
- The clinical claim was based on the ATTR-ACT trial subgroup with ATTR-CM and NYHA class I-II heart failure at baseline, consistent with the requested restriction.

6.6 Details of the ATTR-ACT trial and long-term extension study, B3461045 are provided in Table 3 below.

Table 3: Key trial and study presented in the resubmission

Trial ID	Protocol title/Publication title	Publication citation
ATTR-ACT (B3461028) (NCT01994889)	A multicentre, international, phase 3, double-blind, placebo-controlled, randomised 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).	Report date: 28 August 2018
	Maurer MS et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy.	*New England Journal of Medicine*, 2018; 379(11):1007-1016.
	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.	*Journal of Heart and Lung Transplantation*, 2019; 38(4):S204.
	Hanna M, Damy T, Grogan M, Stewart M, Gundapaneni B, Patterson TA, Schwartz JH, Sultan MB, Maurer MS. Impact of tafamidis on health-related quality of life in patients with transthyretin amyloid cardiomyopathy (from the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial).	*American Journal of Cardiology*. 2021; 141:98-105.
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).	*European Heart Journal,* 2019; 40(Suppl 1):1169.
	Elliott P, Drachman BM, Gottlieb SS, Hoffman JE, Hummel SL, Lenihan DJ, Ebede B, Gundapaneni B, Li B, Sultan MB. Long-term survival with tafamidis in patients with transthyretin amyloid cardiomyopathy.	*Circulation. Heart Failure*, 2022; 15:e008193.

Source: Table 2.2.1, pp50-53 of the resubmission.
Note: Abstracts and poster presentations not listed.

6.7 The key features of the studies are summarised in Table 4.

Table 4: 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)	Randomised, double blind, placebo-controlled, multicentre 30 months	Unclear	18-90 years, ATTR-CM with CV involvement[a]	All-cause mortality, CV mortality, CV hospitalisation, 6MWT, KCCQ-OS, EQ-5D-3L	IPD in the NYHA class I/II subgroup informed mortality, NYHA class and CV hospitalisation transitions, utilities and treatment discontinuation
B3461045 (extension study)	Broad Cohort Tafamidis 20/61 mg (N=116)[b] Tafamidis 80/61 mg (N=230)[b]	~61 months[c] (ongoing)	High	Cohort A Patients completing 30 months treatment in ATTR-ACT; Cohort B Patients with ATTR-CM not enrolled in ATTR-ACT[d]	Safety all-cause mortality and treatment emergent adverse events, CV hospitalisation	Used in sensitivity analyses.

Source: Sections 2.3 and 2.4 of the resubmission; Elliot (2019).
Abbreviations: 6MWT, six minute walk test; ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular; IPD, individual patient data; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score.
[a] Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness ≥ 12 mm.
[b] Includes patients switching from placebo.
[c] ATTR-ACT treatment phase duration and extension study duration.
[d] Cohort B was excluded from the resubmission.

6.8 At the July 2020 meeting the PBAC considered that the ATTR-ACT trial may have been subject to selection bias, and that smaller proportions of patients with baseline NYHA class III heart failure in the tafamidis 20 mg and 80 mg treatment arms, compared to the placebo arm, may have biased trial outcomes in favour of tafamidis (para 6.10, Tafamidis PSD, July 2020 PBAC meeting).

6.9 The March 2021 resubmission argued that the Finkelstein-Schoenfeld method used in the primary analysis minimised the impact of baseline differences in NYHA class and disease severity between treatment arms, and noted that NYHA class was a covariate in statistical models used to analyse other ATTR-ACT endpoints. However, the PBAC considered that use of the Finkelstein-Schoenfeld methodology may not have addressed differences between treatment arms in terms of other known (e.g. NT-proBNP) and unknown prognostic factors, and that the impact of differences between treatments arms on the results of the ATTR-ACT trial remained unclear (para 6.7, Tafamidis PSD, March 2021 PBAC meeting).

6.10 The resubmission argued that much of this potential bias has been removed, given the amended restriction limits initiation and continuing treatment to NYHA class I-II heart failure only. However, given the differences in baseline risk and disease severity between treatment arms in the ATTR-ACT trial, and differences between treatment arms in terms of other known (NT-proBNP) and unknown prognostic factors, the impact of differences between treatment arms on the key results of the ATTR-ACT trial remains unclear.

6.11 Patients in the ATTR-ACT trial tafamidis treatment arms continued treatment into the B3461045 extension study, while patients in the placebo arm were randomised on a 2:1 ratio to initiate tafamidis 80 mg and 20 mg respectively. Blinding of patients and investigators was maintained until a July 2018 protocol amendment added Cohort B (patients with ATTR-CM treated with tafamidis not enrolled in ATTR-ACT) and migrated all patients in Cohorts A and B from tafamidis meglumine 20 mg or 80 mg, to the tafamidis 61 mg free acid formulation. The B3461045 extension study switched to a single arm study design and was unblinded and the risk of bias in the study was high.

6.12 Limited data are available to assess the applicability of the ATTR-ACT trial to the Australian setting. However, age, NYHA class, TTR genotype and ATTRv mutation phenotype have been identified as baseline prognostic indicators for ATTR-CM (Castano et al. 2016; Rapezzi et al. 2009; Siddiqi et al. 2018) and may affect baseline risk. Any differences between the ATTR-ACT study population and the proposed eligible Australian population in the distributions of age, NYHA class, TTR genotype and ATTRv mutation phenotype may result in differences in the absolute benefit of tafamidis. The ESC considered that, from the evidence available, there does not appear to be a substantial difference in baseline demographics and disease characteristics between the ATTR-ACT trial and the proposed PBS population that would significantly impact on the applicability of the trial. The ESC also considered that any difference in treatment effect due to baseline differences would likely be lessened by limiting the PBS population to patients with NYHA class I-II.

Comparative effectiveness

6.13 The results of the ATTR-ACT trial were previously presented in the July 2020, March 2021 and September 2021 submissions, and are summarised below.

6.14 Table 5 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 5: 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, p77 of the July 2020 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.

6.15 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 CV-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%).

6.16 The Finkelstein-Schoenfeld results are consistent with those for individual outcomes. Tafamidis 80 mg demonstrated statistically significant reductions in both all-cause mortality (HR 0.690, 95% CI 0.487, 0.979) and cardiovascular hospitalisations (RR 0.699; 95% CI 0.572, 0.855) compared to placebo. Results for tafamidis 20 mg showed a trend but no statistically significant difference in all-cause mortality (HR 0.715; 95% CI 0.450, 1.137), but a statistically significant reduction in cardiovascular hospitalisations (RR 0.661; 95% CI 0.511, 0.856) compared to placebo.

6.17 For the 6-minute walk test (6MWT), tafamidis was associated with statistically significantly smaller decreases in distance walked from baseline to 30 months, compared to placebo). However, there were larger proportions of placebo patients with incomplete or not properly administered 6MWTs in the ATTR-ACT trial and differences between treatment arms may not reflect differences in patient functional capacity.

6.18 Patients treated with tafamidis reported statistically significantly smaller mean reductions in the Kansas City Cardiomyopathy Questionnaire-overall score (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. Similarly, patients treated with tafamidis reported smaller mean reductions in EQ-5D-3L compared to placebo.

6.19 The resubmission presented subgroup analyses by pre-specified subgroups stratified at randomisation of the ATTR-ACT trial (NYHA classification; TTR genotype). Tests for treatment effect interaction indicated that NYHA class is a treatment effect modifier for cardiovascular hospitalisation, with results indicating an increased risk of hospitalisation in patients with NYHA class III treated with tafamidis versus placebo. There was no statistically significant difference in all-cause mortality or cardiovascular mortality between patients treated with tafamidis versus placebo, in the NYHA III subgroup. Additional *post hoc* subgroup analyses showed a consistent pattern of decreased tafamidis treatment effect with increasing disease severity stratified by NYHA class and 6MWT quartiles. The ESC considered this area of uncertainty was appropriately addressed with the revised PBS restrictions proposing to exclude patients with NYHA class III.

6.20 *Post hoc* analyses of the ATTR-ACT and B3461045 long term extension data for all-cause mortality by NYHA baseline class (NYHA class I/II and III) for the August 2019 and March 2020 data cuts (previously considered by the PBAC at the March 2021 and September 2021 meetings) and updated August 2021 data cut showed statistically significant reduction in all-cause mortality for patients with baseline NYHA class I/II in the tafamidis 80/61 mg treatment arm compared to the placebo/tafamidis arm (HR: 0.502; 95%CI: 0.346, 0.727, August 2021 data cut).

6.21 The tafamidis 80/61 mg treatment arm excluded patients randomised to tafamidis 20 mg, while the placebo/tafamidis treatment arm included patients switching to tafamidis 20 mg or 80 mg from placebo. The flow of patients through the B3461045 study was not adequately reported, and it is unclear whether patients in the placebo/tafamidis treatment arms received ≥18 months of treatment, which was the duration of tafamidis treatment before differences in all-cause mortality were observed in Kaplan-Meier plots of all-cause mortality in the ATTR-ACT trial. Given the differences in mixed tafamidis dose intensity, duration of treatment and drug exposure, the results of the *post hoc* subgroup analyses should be interpreted with caution.

6.22 The ESC noted that longer-term data from the extension study provided in the submission appeared to support a small superiority in efficacy of the tafamidis meglumine 80 mg dose over the 20 mg dose.

Nonrandomised studies

6.23 The resubmission presented the results of 11 nonrandomised studies to provide evidence of the observed benefit of tafamidis in clinical practice, including measures of functional capacity, cardiovascular markers, cardiovascular outcomes and mortality as well as tafamidis usage patterns and adherence. A literature search for the nonrandomised studies was not presented and details of how the studies were selected were not provided.

6.24 The results of the nonrandomised studies generally showed that patients treated with tafamidis experienced some benefit compared to patients not treated with tafamidis. However, given the lack of a control group in the single arm studies (Fx1B-201/303), the allocation bias strongly favouring tafamidis identified in all studies reporting comparative analyses (Amaka 2022, Bezard 2021, Hussain 2022, Ochi 2022, Sarkar 2022), the lack of reporting or use of the lower tafamidis dose strength in 7 studies (Fx1B-201/303, Amaka 2022, Bezard 2021, Hussain 2022, Korczyk 2022, Sarkar 2022), and the lack of sufficient data for evaluation in 2 studies (Korczyk 2022, Rettl 2021), the results of the nonrandomised studies should be interpreted with caution. The ESC considered that these nonrandomised studies may be unreliable and not applicable to the eligible Australian population.

Comparative harms

6.25 Safety data for the ATTR-ACT trial are unchanged from the previous submissions. Safety outcomes for treatment emergent adverse events in the B3461045 long-term extension study were not reported.

6.26 Table 6 summarises the proportions of patients experiencing key treatment emergent adverse events in the ATTR-ACT trial.

Table 6: Summary of key adverse 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: Tables 2.5.1 and 2.5.2, pp69-70 of the resubmission; Tables 2.5.16, p113 and 2.5.17, pp114-116 of the July 2020 submission.
Abbreviations: AEs, adverse events; ATTRv, variant (mutated) transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; SAEs serious adverse events.

6.27 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.

6.28 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%).

6.29 No new important identified or potential safety risks were identified in the most recent tafamidis periodic safety update report (PSUR) for the period 16 May 2022 to 15 November 2022, and no new safety risks identified in ongoing longer-term safety studies. Interim results of pre-specified safety outcomes for treatment emergent adverse events in the B3461045 long-term extension study were not reported.

6.30 The ESC noted that the safety data for tafamidis were still based on relatively few patients.

Benefits/harms

6.31 Benefits and harms based on the results of the direct ATTR-ACT trial are unchanged from the previous submissions. Insufficient information was available to assess benefits and harms in the relevant subgroup of patients with NYHA class I/II at baseline.

6.32 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 additional patients will be alive at 30 months.
- 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

6.33 The resubmission described tafamidis 61 mg (equivalent to tafamidis meglumine 80 mg), as superior in terms of effectiveness and inferior in terms of safety, compared to standard management of ATTR-CM heart failure.

6.34 The PBAC previously accepted the clinical claim that tafamidis is superior in terms of efficacy and inferior in terms of safety compared with standard management (paras 7.7-7.9, Tafamidis PSD, March 2021 PBAC meeting). The PBAC considered that previous concerns regarding the magnitude of benefit in the Australian PBS population were lessened by the revised restriction limiting initiation of tafamidis to NYHA class I/II, as well as additional data presented in the March 2021 submission; and that although a moderate amount of uncertainty remained, the PBAC recognised that tafamidis provided a substantial and clinically relevant improvement in efficacy overall (para 7.8 Tafamidis PSD, March 2021 PBAC meeting).

6.35 The ESC considered that the clinical claim of superior efficacy and inferior safety for tafamidis compared with standard management of ATTR-CM heart failure remained supported.

6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable.

6.37 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.38 The resubmission presented a modelled economic evaluation of tafamidis added to standard management compared to standard management alone for the treatment of ATTR-CM. The economic evaluation was based on the ATTR-ACT trial with additional

modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

6.39 For the September 2021 Early Resolution submission, a number of changes had been made to the model presented in the March 2021 submission:

- Corrections to errors in hospitalisation costs, health state costs, and diagnosis costs, identified during the March 2021 evaluation.
- Allowing for increasing mortality over time and a reduced treatment effect for tafamidis on mortality (composite outcome of death/transplant/VAD) to attempt to account for treatment-related discontinuation, presented in the March 2021 pre-PBAC response.
- Incorporating treatment discontinuation for patients in the tafamidis arm with persistent NYHA class III/IV (i.e. in NYHA class III/IV for more than one consecutive cycle).
- A reduction in the effective DPMQ for tafamidis (from $ to $ for the first 3 years and $ for subsequent years).

6.40 The key changes to the economic model between the September 2021 and the current resubmissions are:

- Updated data were used to inform the time to treatment discontinuation curve (based on the ATTR-ACT long-term extension study).
- Hospitalisation costs were updated using more recent AR-DRG cost weights.
- Diagnosis costs were applied to both the tafamidis and standard management arms (previously only applied to the tafamidis arm), to reflect increased awareness of ATTR-CM.
- A reduction in the effective DPMQ for tafamidis ($ for the first 3 years and $ for subsequent years).
- A dose intensity of 97.67% was applied to account for non-adherence with tafamidis treatment (previous submissions assumed perfect adherence).

6.41 Table 7 summarises the key components of the economic evaluation.

Table 7: Key components of the economic evaluation

Component	Description
Treatments	Tafamidis plus standard management; standard management alone
Time horizon	20 years versus 2.5 years in the ATTR-ACT trial.
Outcomes	Life years; quality adjusted life years
Methods used to generate results	Markov state transition model
Health states	9 health states - NYHA class I/II, no CV hospitalisation (on treatment) - NYHA class I/II, CV hospitalisation (on treatment) - NYHA class I/II, no CV hospitalisation (off treatment) - NYHA class I/II, CV hospitalisation (off treatment) - NYHA class III/IV, no CV hospitalisation (on treatment) - NYHA class III/IV, CV hospitalisation (on treatment) - NYHA class III/IV, no CV hospitalisation (off treatment) - NYHA class III/IV, CV hospitalisation (off treatment) - Dead
Cycle length	6 months
Transition probabilities	Individual patient data from the ATTR-ACT trial were used to derive transition probabilities for movement between NYHA classes I/II and II/IV, CV-related hospitalisations, and death over the first five 6-month cycles. Transition probabilities beyond the 30-month duration of the ATTR-ACT trial were based on weighted averages of the first five 6-month cycles. Death transitions were assumed to increase by 5.3% per 6-month cycle from cycle 7, consistent with the sensitivity analysis presented in the March 2021 pre-PBAC response. The number of hospitalisations per hospitalised patient was derived for each treatment arm based on the average annual hospitalisations per patient for those alive at Month 30 from the ATTR-ACT trial, adjusted for the likelihood of being hospitalised for NYHA class I/II versus class I/II/III patients, adjusted for the 6-monthly cycle length, and divided by the proportion of patients hospitalised. The probability of discontinuation in the tafamidis arm was estimated by fitting an exponential curve to ATTR-ACT data for the subset of patients with NYHA class I/II at baseline. The relative benefit of tafamidis in reducing the risk of death was reduced from cycle 7 proportional to treatment-related discontinuation, consistent with the sensitivity analysis presented in the March 2021 pre-PBAC response.
Utility values	Utilities were based on a *post hoc* reanalysis of EQ-5D-3L data (UK value set) from the ATTR-ACT trial by treatment arm and NHYA class. No additional disutility assumed for cardiovascular hospitalisation.
Costs	Diagnostic costs were estimated based on expert advice on health resource use from a sponsor-commissioned physician survey and costings based on MBS and AR-DRG items. Costs were applied to both the tafamidis and standard management arms. Tafamidis drug costs estimated based on proposed effective DPMQs. Cardiovascular hospitalisation costs estimated as the weighted average of 93 cardiovascular-related AR-DRG items. Cost estimates inflated using the AIHW Total Health Price Index. Disease management costs were estimated from published studies (Ademi 2014, Ford 2012). Cost estimates inflated using the AIHW Total Health Price Index. Terminal care costs were estimated based on the assumption that half of all deaths would be preceded by a cardiovascular-related hospitalisation.

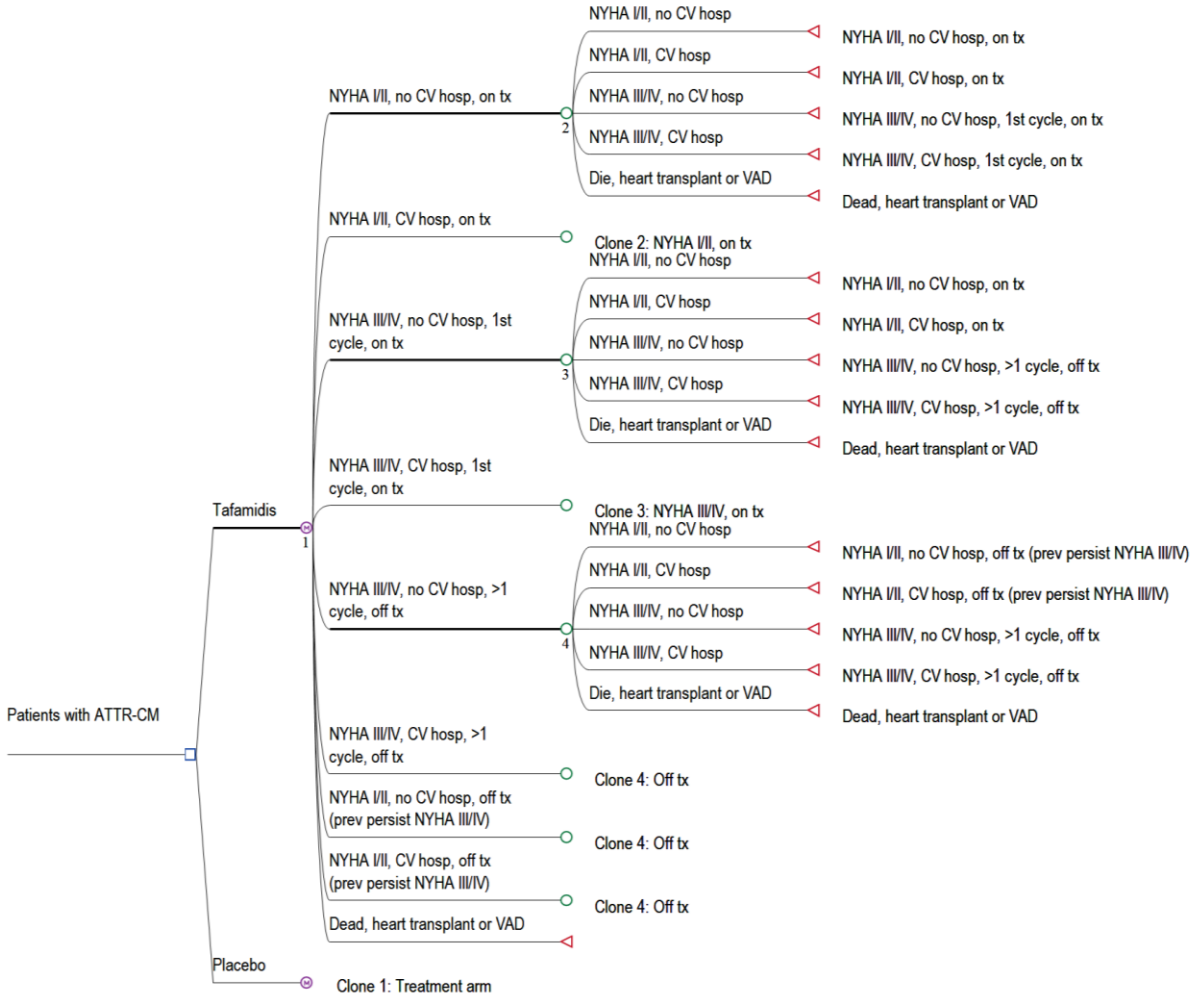
Source: Table 3.1.4, p221 and Section 3 of the current resubmission.

Abbreviations: AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; CV, cardiovascular; DPMQ, dispensed price for maximum quantity; MBS, Medicare Benefits Schedule; NYHA, New York Heart Association

6.42 The model structure was revised in the current resubmission (and in the September 2021 resubmission) to incorporate tafamidis treatment discontinuation for patients with persistent NYHA class III heart failure. This necessitated the inclusion of additional health states to track the number of cycles in NYHA III/IV health states, and on/off treatment.

6.43 The revised model structure is illustrated in Figure 1 below.

Figure 1: Model structure diagram



Source: Constructed during the evaluation, based on Figure 3.1.2, p223 of the resubmission.
Abbreviations: CV, cardiovascular; hosp, hospitalisation; NYHA, New York Heart Association; persist, persistent; prev, previous; tx, treatment.

6.44 Patients begin the model in the 'NYHA class I/II, no cardiovascular hospitalisation' health state. During each 6-month cycle, patients can transition to another NYHA class and/or experience hospitalisation, or die.

6.45 The underlying transition probabilities for movement between NYHA class I/II and III/IV, cardiovascular-related hospitalisation and death used in the resubmission were unchanged from the March 2021 resubmission, with transition probabilities for the first five 6-monthly cycles based on individual patient data from the subgroup of

patients from the ATTR-ACT trial with NYHA class I/II at baseline; and transition probabilities beyond 30 months based on weighted average estimates of the first 5 cycles of transitions from the ATTR-ACT trial. The resubmission assumed that the composite outcome of death, cardiac transplant, or VAD insertion was composed of deaths only, given advice from the sponsor's expert panel indicating that the target PBS population is highly unlikely to undergo cardiac transplantation or insertion of a VAD.

6.46 The use of composite NYHA class/hospitalisation health states, combined with individual cycle transitions over the first five 6-monthly model cycles, resulted in data sparseness issues. The ESC previously considered that it may be more appropriate to apply state-specific cardiovascular hospitalisation rates to inform the estimation of health state costs (including exploration of cardiovascular hospitalisation rates increasing over time), rather than specifying separate cardiovascular hospitalisation states (para 6.57, Tafamidis PSD, March 2021 PBAC meeting).

6.47 Consistent with the requested restriction, patients in the tafamidis arm with persistent NYHA class III/IV heart failure (i.e. patients who remain in a NYHA class III/IV health state for more than 1 consecutive cycle) discontinue treatment. The resubmission stated that patients who discontinue tafamidis due to persistent NYHA class III/IV heart failure were assumed to have the same transition probabilities as patients in the standard management arm. However, the discontinuation of patients with disease progression to persistent NYHA III/IV, that was first implemented in the September 2021 submission, was incorrectly applied in the economic model. When corrected, the discontinuation of these patients has a minimal impact on the model.

6.48 The use of average transition probabilities for cycles 6+ of the model resulted in constant transition probabilities over time for death, NYHA class transitions, and hospitalisation; which was previously considered inappropriate, as disease progression/cardiovascular hospitalisations and mortality would generally be expected to increase with age and duration of disease (para 6.53, Tafamidis PSD, March 2021 PBAC meeting). The current model incorporates a 5.3% increase in mortality per 6-monthly cycle from cycle 7 onwards, based on mortality data from the 2018 AIHW GRIM books. No adjustments were made to other transition probabilities. The 5.3% mortality adjustment was previously incorporated into a sensitivity analysis presented in the March 2021 pre-PBAC response and the September 2021 submission's base case model. The PBAC previously considered that, while this analysis represented a crude adjustment for mortality, it may be reasonable in the absence of better data (para 7.10, Tafamidis PSD, March 2021 PBAC meeting). The ESC considered that although mortality was adjusted, constant NYHA class transitions and hospitalisations over the 20 year time horizon may not be plausible and this favours tafamidis. The pre-PBAC response provided a revised model including a sensitivity analysis which applied waning of treatment effect to hospitalisations and NYHA progression. Using the revised model provided with the pre-PBAC response the ICER

increased by 9% to $135,000 to < $155,000/QALY (with the revised price for years 4 onwards applied).

6.49 In the March 2021 model, treatment discontinuation rates were applied to drug costs only, with no impact on survival, NYHA class, or cardiovascular hospitalisations. The PBAC considered maintenance of the tafamidis treatment effect following treatment-related discontinuation was inappropriate, given increasing proportions of patients discontinuing over time, with longer durations without therapy (para 6.56, Tafamidis PSD, March 2021 PBAC meeting). To address this issue, the current model adjusts the risk of death in the tafamidis arm by applying standard management arm risks to the proportion of patients who discontinued tafamidis treatment from cycle 7 (as in the September 2021 submission's base case model). The PBAC previously considered that this adjustment did not fully correct the issue, as no adjustment was made to any other transition probabilities, and tafamidis-treated patients who discontinued treatment maintained a treatment benefit in terms of hospitalisation and NYHA progression/regression, which generated an indirect mortality benefit (paras 6.56, 7.10, Tafamidis PSD, March 2021 PBAC meeting). Given that on/off treatment health states were included in the resubmission's model to incorporate patients discontinuing tafamidis due to persistent NYHA class III/IV heart failure, it is unclear why a different approach was used for tafamidis patients with treatment-related discontinuation. The PSCR argued that the modelled economic evaluation drew ITT data directly from the pivotal studies and therefore treatment effects (changes to the risks of death, hospitalisation and movement among NYHA classes) already accounted for treatment discontinuation. However, the ESC considered that use of the 2.5 years of trial data would not capture treatment effects over the full 20-year time horizon in the model and noted that this remained an issue in the resubmission.

6.50 The transition probabilities include transitions from NYHA class III/IV to NYHA class I/II over the duration of the model. At the March 2021 meeting, the PBAC considered that a proportion of patients may experience an improvement from NYHA class III/IV to class I/II initially, but this was unlikely to continue for the duration of the model (para 6.55, Tafamidis PSD, March 2021 PBAC meeting). A sensitivity analysis was conducted during the evaluation removing transitions from NYHA class III/IV to I/II after 2.5 years (see Table 9 below).

6.51 The March 2021 and September 2021 submissions assumed that diagnostic costs would only be incurred due to the availability of tafamidis, and costs were not applied to the standard management arm. The current resubmission argued that awareness of ATTR-CM has increased over time, as has diagnosis of the condition; and that, even in the absence of a disease-modifying treatment, diagnosis is important, as optimisation of a patient's standard management will result in improvement of their condition. As a result, the same diagnostic costs are applied to the tafamidis and standard treatment arms of the model.

6.52 Compared with the March 2021 model base case, allowing for increased mortality over time and introducing a waning treatment effect on mortality to account for

tafamidis treatment-related discontinuation (which both increased the ICER), introducing tafamidis discontinuation for patients with persistent NYHA class III/IV and reducing the proposed effective price of tafamidis (which both decreased the ICER), had the largest impact on the September 2021 model base case. However, discontinuation of tafamidis patients with persistent NYHA stage III/IV heart failure was not correctly implemented in either the September 2021 model or in the current submission.

6.53 Compared with the September 2021 model base case, applying diagnosis costs to both treatment arms rather than the tafamidis arm alone (which reduced the ICER) and correcting the resubmission's error in the implementation of treatment discontinuation for patients with persistent NYHA class III/IV heart failure during the evaluation (which increased the ICER), had the largest impact on the current resubmission's model.

6.54 The results of the corrected modelled economic evaluation are summarised in Table 8.

Table 8: Results of the economic evaluation

Component	Tafamidis	Standard management	Increment
Costs	$[1]	$51,684	$[2]
Life years	5.6735	4.6241	1.0494
QALYs	4.1630	3.1923	0.9708
Incremental cost per life year gained			**$[2]**
Incremental cost/QALY gained			**$[3]**

Source: Constructed during the evaluation using the 'Tafamidis Economic Model March 2023' spreadsheet provided with the resubmission
Abbreviation: QALY, quality adjusted life year.
Note: Results were updated during the evaluation to correct for the misapplication of diagnosis costs (based on costs in the September 2021 model, with half of the costs attributed to the tafamidis arm and half to the standard management arm; this does not affect the ICER, as costs were applied to both treatment arms), and transitions from NYHA class I/II off-treatment were corrected to be based on standard management probabilities, rather than tafamidis on-treatment probabilities.
The redacted values correspond to the following ranges:
[1] $155,000 to < $255,000
[2] $115,000 to < $135,000
[3] $135,000 to < $155,000

6.55 Based on the economic model presented in the resubmission, treatment with tafamidis was associated with an incremental cost per QALY gained of $135,000 to < $155,000 (uncorrected estimate $95,000 to < $115,000) compared to standard management for the treatment of patients with ATTR-CM. This compares with an incremental cost per QALY gained of $135,000 to < $155,000 (unevaluated/uncorrected) in the September 2021 resubmission and $155,000 to < $255,000 (uncorrected estimate $155,000 to < $255,000) in the March 2021 resubmission.

6.56 The incremental cost per QALY gained of $135,000 to < $155,000 was based on a tafamidis price of $ for the first 3 years, and $ for subsequent years. Using the pre-PBAC proposed price for years 4 and onwards the ICER decreased to $115,000 to < $135,000/QALY gained. This cost-effectiveness reflects a cohort who begin treatment with tafamidis when first listed on the PBS. The ICER of a cohort of patients who begin treatment at a later time point would be lower, with less (or no)

treatment at the higher price. Sensitivity analyses using the higher and lower proposed prices over the entire model duration are presented in Table 9 below.

6.57 The PBAC previously considered that an ICER of $80,000 per QALY gained for tafamidis versus standard management would be more acceptable (paras 7.11, 7.13, Tafamidis PBAC PSD, March 2021 PBAC meeting; para 10.4, Tafamidis PBAC PSD, March 2021 PBAC meeting with September 2021 addendum). The resubmission stated that the sponsor is unable to meet the $80,000 ICER, but noted that reductions in the published and effective prices for tafamidis were proposed in the resubmission, which are the lowest prices proposed to date. The proposed effective prices represent reductions of % (for the first 3 years of listing) and % (for subsequent years) compared to the effective prices proposed in the September 2021 submission. The resubmission also noted that a number of treatments for rare diseases have received positive recommendations with higher ICERs (for example, $155,000 to <$255,000 per QALY gained, $255,000 to < $355,000 per QALY gained). The PSCR stated that the ICERs achieved for tafamidis are in the order of those for cystic fibrosis, recommended by the PBAC and PBS-listed in 2021 and 2022.

6.58 The price of tafamidis would have to be $ over the model duration to achieve an ICER of $80,000 per QALY gained, assuming no other changes to the model. This represents a % reduction on the proposed effective DPMQ for the first 3 years and a % reduction on the proposed effective DPMQ for subsequent years.

6.59 In the corrected model, 36.0% of incremental costs and 82.1% of incremental QALYs are accrued in the extrapolated period.

6.60 For every patient treated with tafamidis versus standard management and followed up for 20 years, the economic evaluation revised during the evaluation (without discounting) estimated that there would be:

- Additional tafamidis drug costs of $ with additional disease management costs of $1,385.
- Additional survival of 1.4 years, with more time spent in NYHA class I/II.
- 1.1 fewer cardiovascular hospitalisations.
- Decreased costs for hospitalisation ($11,286) and terminal care ($217).

6.61 The results of key sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised in Table 9.

Table 9: Results of key sensitivity analyses

	Incremental cost	Incremental QALYs	ICER	% change from base case
Base case	[redacted]	0.9708	[redacted]2	-
Discount rate (base case: 5% for benefits and costs)				
3.5% for costs and benefits	[redacted]	1.0440	[redacted]1	-4.3%
0% for costs and benefits	[redacted]	1.2534	[redacted]1	-14.1%
Time horizon (base case: 20 years)				
10 years	[redacted]	0.8775	[redacted]2	+9.1%
15 years	[redacted]	0.9636	[redacted]2	+0.7%
Diagnostic phase (base case: 92.246 patients treated per 1,000 patients identified based on 2021 utilisation estimates; availability of tafamidis has no impact on diagnosis – costs applied to both treatment arms)				
Diagnosis costs applied to tafamidis arm only	[redacted]	0.9708	[redacted]2	+11.5%
100% diagnosis costs tafamidis; 50% placebo	[redacted]	0.9708	[redacted]2	+5.8%
Patient population (base case: 100% NYHA class I/II at baseline)				
68% NYHA class I/II; 32% NYHA class III/IV at baseline	[redacted]	0.5499	[redacted]3	+20.1%
Underlying transition probabilities (base case: six-monthly transitions derived using IPD from ATTR-ACT trial; missing data deleted; beyond trial duration based on weighted average of the 5 trial-based 6-monthly cycles)				
Cycles 1-5, 6+: weighted average of cycles 1-5; missing data deleted	[redacted]	0.9332	[redacted]2	+2.1%
Cycles 1-5, IPD; cycles 6+: weighted average of cycles 1-5; LOCF to impute missing data	[redacted]	0.8507	[redacted]2	+9.0%
Cycles 6+: based on data from extension study	[redacted]	0.7020	[redacted]2	+10.3%
Adjustments to underlying transition probabilities (base case: transitions from NYHA class III/IV to NYHA class I/II occur over the model duration; risk of death assumed to increase by 5.3% per 6-month cycle from cycle 7; a waning tafamidis treatment effect is applied from cycle 7 to account for tafamidis treatment-related discontinuation)				
No transitions from NYHA class III/IV to NYHA class I/II from cycle 6[a]	[redacted]	0.8260	[redacted]2	+7.6%
Remove increasing mortality over time	[redacted]	1.1477	[redacted]1	-13.8%
Remove adjustment to tafamidis treatment effect on mortality to account for treatment-related discontinuations	[redacted]	1.1598	[redacted]1	-13.6%
Remove discontinuation due to persistent NYHA class III/IV	[redacted]	1.3245	[redacted]1	-1.7%
CV hospitalisations per hospitalised patient (base case: 1 for tafamidis arm; 1.35 for standard management arm)				
1 for both treatment arms	[redacted]	0.9708	[redacted]2	+5.2%
Utility values (base case: utilities based on a post hoc reanalysis of EQ-5D-3L data with UK weights from ATTR-ACT trial by treatment arm and NYHA class; distribution between NYHA I and II and NYHA III and IV assumed)				
Treatment independent NYHA utility values (based on Ademi 2014 publication)	[redacted]	0.8371	[redacted]3	+16.0%
Treatment independent NYHA utility values (based on standard management arm)	[redacted]	0.9035	[redacted]2	+7.4%
Treatment independent NYHA utility values (based on tafamidis arm)	[redacted]	0.9024	[redacted]2	+7.6%
Treatment costs (base case: proposed effective tafamidis DPMQ $[redacted] years 1-3, $[redacted] years 4+; treatment adherence 97.67%)				
Price same as first 3 years ($[redacted])	[redacted]	0.9708	[redacted]2	+8.6%
Price same as subsequent years ($[redacted])	[redacted]	0.9708	[redacted]4	-17.5%
Pre-PBAC price ($[redacted]) for year 4+	[redacted]	0.9708	[redacted]b 1	-3.1%
Pre-PBAC price ($[redacted]) for all years	[redacted]	0.9708	[redacted]4	-26.9%

Source: Constructed during the evaluation using the 'Tafamidis Economic Model March 2023' spreadsheet provided with the resubmission, with errors in diagnosis costs corrected and transitions from NYHA class I/II off-treatment corrected to be based on standard management probabilities, rather than tafamidis on-treatment probabilities.

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; IPD, individual patient data; LOCF, last observation carried forward; NYHA, New York Heart Association; QALY, quality adjusted life year.

[a] Transitions to NYHA class I/II without hospitalisation allocated to NYHA class III/IV without hospitalisation; transitions to NYHA class I/II with hospitalisation allocated to NYHA class III/IV with hospitalisation.

[b] The pre-PBAC response reported this ICER as $115,000 to < $135,000 per QALY gained.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$135,000 to < $155,000*

[3] *$155,000 to < $255,000*

[4] *$95,000 to < $115,000*

[5] *$75,000 to < $95,000*

6.62 The sensitivity analyses indicate that the model is most sensitive to the application of diagnosis costs to the standard management arm, the inclusion of patients with NYHA class III/IV at baseline, the source of the underlying transition probabilities, the price of tafamidis, and the use of health state utilities without treatment-related effects.

6.63 The ESC noted the sensitivity analyses do not adequately capture the uncertainty associated with the model, as they do not explore the impact of tafamidis treatment-related discontinuation on risks of hospitalisation and NYHA class progression/regression, nor do they account for increasing disease progression over time, except for risk of death.

6.64 The PBAC considered that at a DPMQ of $[redacted] (the price proposed for the initial 3 years post listing), the ICER of $135,000 to < $155,000 per QALY was unacceptably high and uncertain. Notwithstanding the remaining uncertainty in the modelled cost-effectiveness estimates, the PBAC considered that tafamidis would be acceptably cost-effective based on a cost no higher than a DPMQ of $[redacted] (ICER of approximately $95,000 to < $115,000 per QALY), the price proposed in the pre-PBAC response for years 4-6. This was in the context of a high unmet clinical need in a relatively small population.

Drug cost/patient/year

6.65 A comparison of tafamidis use between the trial setting, economic model and budget impact model is presented in Table 10.

Table 10: Drug cost per patient per year for tafamidis

	Trial	Economic model	Financial estimates
Daily dose	Tafamidis meglumine 20 mg or 80 mg	Tafamidis 61 mg	Tafamidis 61 mg
Cost per 30 tablet pack (effective DPMQ)	-	$ (Years 1-3) $ (subsequent years)	$ (Years 1-3) $ (Years 4-6)
Adherence	98.2% (> 80% adherence)	97.67%	100%
Number of scripts per year	-	11.90 (=365.25/30×97.67%)	12.18 (=365.25/30)
Cost per year	-	$ (Years 1-3) $ (subsequent years)	$ (Years 1-3) $ (Years 4-6)
Proportion of patients on treatment	At 30 months, 19.7% of patients in the pooled tafamidis arm of the ATTR-ACT trial had discontinued.	Year 1: 100%[a] Year 2: 82% Year 3: 63% Year 4: 46% Year 5: 34% Year 6: 25%	Year 1: 100%[b] Year 2: 63% Year 3: 40% Year 4: 25% Year 5: 16% Year 6: 10%

Source: Constructed during the evaluation using 'Tafamidis Economic Model March 2023' and 'UCM-Release-3-Workbook-v1081 - Vyndamax - tafamidis - March 2023' spreadsheets provided with the resubmission.

[a] Calculated during the evaluation by multiplying the proportion of patients in an on-treatment health state (patients who had not discontinued due to persistent NYHA class III/IV heart failure) by estimates from the drug survival curve (used to estimate tafamidis treatment-related discontinuation).

[b] Proportions of patients alive and on treatment at the start of each year, assuming a fixed cohort from Year 1. The estimated annual mortality of 11% was based on the number of patients who died in the tafamidis 80 mg arm of the ATTR-ACT trial over the 30 month duration, adjusted to derive an annual estimate (28%×12/30). The annual discontinuation rate of 26% was based on discontinuations due to persistent NYHA class III or NYHA class IV heart failure or discontinuations due to other reasons, based on data from the ATTR-ACT trial.

6.66 The annual cost of tafamidis is $ per patient for the first 3 years of listing (based on the proposed effective DPMQ of $, 12.175 scripts and 97.67% adherence); and $ per patient in subsequent years (based on the proposed effective DPMQ of $). The cost in subsequent years was reduced to $ based on effective DPMQ proposed in the pre-PBAC response ($).

6.67 The different approaches to estimating the proportions of patients moving to NYHA class III/IV and death in the economic and budget impact models lead to different proportions of patients remaining on tafamidis treatment over time. In the economic model, transitions were based on outcomes for each 6-month cycle over the 30-month duration of the ATTR-ACT trial, with different estimates calculated based on NYHA class (I/II or III/IV) and hospitalisation status (with or without hospitalisation), resulting in sparse data issues. Estimates of mortality in the budget impact model were based on all patients over the 30-month duration of the ATTR-ACT trial, while transitions to NYHA class III/IV were based on all patients in NYHA class I/II who transitioned to NYHA class III/IV in the first 2 years of the trial (27% and 29%), rounded up to an annual estimate of 30%. No justification was provided in the resubmission for the different approach used in the financial estimates.

Estimated PBS usage & financial implications

6.68 This submission was not considered by DUSC. The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing tafamidis on the PBS.

6.69 The resubmission used the same overall approach as the March 2021 and September 2021 submissions, with some adjustments:

- Consistent with the September 2021 resubmission, the current resubmission updated the estimated use and financial impact of listing tafamidis on the PBS for the revised target population (NYHA class I-II heart failure and non-persistent class III heart failure), including estimated proportions of patients likely to transition from NYHA class I/II to NYHA classes III and IV, and the proportion of patients likely to remain in persistent NYHA class III heart failure.
- The resubmission updated the estimated proportions of patients diagnosed with ATTR-CM, uptake of tafamidis in the eligible population, and selected MBS costs associated with the listing of tafamidis on the PBS and hospital costs associated with diagnosis of ATTR-CM (myocardial biopsy by cardiac catheterisation).
- The resubmission proposed a revised RSA based on the updated estimates.

6.70 Key inputs relied on in the financial estimates are summarised in Table 11.

Table 11: Key inputs for financial estimates

Data	Value and source	Comment
Prevalence of ATTRwt related cardiomyopathy	Using the ABS population forward estimates (3222.0 Series B), the resubmission applied factors for the proportions of population with heart failure by age and sex derived from Liew et al. (2020) a Study of Heart failure in the Australian Primary carE setting (SHAPE), and the prevalence of amyloid deposition in the Australian population derived from Cuscaden et al. (2020), an Australian study of images taken from the medical records of patients undergoing bone scans for non-cardiac reasons.	This was unchanged from the March 2021 submission. Liew et al. (2020) was based on general practice 'all patients' data rather than 'active' patients (patients with 3 or more visits per year), with high rates of itinerant attendances and low rates of chronic conditions recorded, and most likely underestimated rates of heart failure. Cuscaden et al. (2020) was based on incidental findings in a small number of patients (n=15) undergoing scintigraphy for non-cardiac indications, and most likely underestimates the prevalence of amyloid disposition in heart failure.
Prevalence of ATTRv related cardiomyopathy	Gertz and Dispenzieri, 2020, a systematic review of systemic amyloidosis diagnosis, prognosis, and therapies, estimated a prevalence of 5.2 cases per million persons.	Unchanged from the March 2021 submission. The estimates most likely underestimate the true prevalence, due to poor recognition and diagnosis rates for amyloidosis.
Proportions of patients diagnosed with ATTR-CM	Assumption. Year 1 - 50%; Year 2 - 60%; Year 3 - 70%; Years 4-6 - 80%	The proportions of patients diagnosed are higher than estimated in the March 2021 and September 2021 submissions (30% in Year 1, increasing 10% each year to 80% in Year 6). The resubmission stated that diagnosis rates are increasing despite the unavailability of disease modifying treatments. Published estimates of ATTR-CM prevalence account for under-diagnosis, and application of this factor may reduce the population unnecessarily. This was inconsistent with estimates used to calculate diagnosis costs in the economic model, which were unchanged from the March 2021 and September 2021 submissions.

Data	Value and source	Comment
Proportions of patients diagnosed with NYHA class I-II	Based on Figure 2.7.1 of the resubmission, proportion patients with NYHA class I-II heart failure in the ATTR-ACT trial. Year 1-2 - 70%; Year 3-6 - 75%	The resubmission assumed the proportion of patients diagnosed with NYHA class I-II will increase over time. The same pattern of increased diagnosis was used in the September 2021 submission.
Uptake of tafamidis	Assumed. Year 1 - 60%; Year 2 - 65%; Year 3 - 70%; Years 4-6 - 75%	This was higher than the rate of uptake assumed in the September 2021 submission (50% in Year 1, increasing 5% each year to 75% in Year 6).
Discontinuation of tafamidis	37% per year: including discontinuations due to persistent NYHA class III heart failure (22%), transition to NYHA class IV heart failure (1%), any other reason (3%), and mortality (11%), derived from the ATTR-ACT trial individual patient data.	Discontinuations reported in the randomised clinical trial may not be realised in the Australian setting. In addition, the estimated overall discontinuations in the financial estimates were substantially higher than observed in the economic model (Table 10 above).
Persistent NYHA class III heart failure	22% per year: calculated from 6 monthly transitions between NYHA classes in the ATTR-ACT trial.	The calculated proportions of patients with persistent NYHA class III heart failure may not be reasonable, given average transitions over 6 months intervals were used as surrogate measures for longitudinal persistence of heart failure symptoms. In addition, the proportions of patients transitioning from NYHA class I-II to class III heart failure used in the calculation inappropriately included the small numbers of patients transitioning to NYHA class IV, and overestimated the proportion of patients discontinuing tafamidis due to disease progression.

Source: Compiled during the evaluation based on Utilisation and cost model - tafamidis provided with the resubmission. Values unchanged since the March 2021 or September 2021 submissions shaded blue.
Abbreviations: ABS, Australian Bureau of Statistics; ATTR-CM, cardiac transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild type transthyretin amyloidosis; DPMQ, dispensed price for maximum quantity; NYHA, New York Heart Association; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

6.71 Table 12 summarises the estimated net cost of tafamidis to the PBS/RPBS and MBS in the current resubmission.

Table 12: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][2]
Net cost to PBS/RPBS	[redacted][4]	[redacted][6]	[redacted][7]	[redacted][6]	[redacted][6]	[redacted][5]
Net cost to MBS	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Net cost to PBS/RPBS/MBS	[redacted][4]	[redacted][6]	[redacted][7]	[redacted][6]	[redacted][6]	[redacted][5]
Net cost to PBS/RPBS, revised pre-PBAC price for yr4+	[redacted][4]	[redacted][6]	[redacted][7]	[redacted][6]	[redacted][5]	[redacted][4]
Net cost to PBS/RPBS/MBS, revised pre-PBAC price for yr4+	[redacted][4]	[redacted][6]	[redacted][7]	[redacted][6]	[redacted][5]	[redacted][4]
March 2021 submission						
Net cost to PBS/RPBS	[redacted][4]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
Net cost to PBS/RPBS/MBS	[redacted][4]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]	[redacted][9]
September 2021 submission						
Net cost to PBS/RPBS	[redacted][11]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]
Net cost to PBS/RPBS/MBS	[redacted][11]	[redacted][4]	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]

Source: Tables 4.1.2, pp261-262, 4.2.1, p263, 4.2.2, pp263-264, 4.2.3, p264, 4.2.8, p266, 4.2.9, p267 and 4.2.10, p267 of the resubmission; Tafamidis March 2021 submission; Tafamidis September 2021 submission. Values unchanged since the March 2021 or September 2021 submissions shaded blue.

Abbreviations: ATTR-CM, cardiac transthyretin amyloidosis; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis.

The redacted values correspond to the following ranges:

[1] 500 to <5,000
[2] 5,000 to < 10,000
[3] 10,000 to < 20,000
[4] $20 million to < $30 million
[5] $30 million to < $40 million
[6] $40 million to < $50 million
[7] $50 million to < $60 million
[8] $80 million to < $90 million
[9] $100 million to < $200 million
[10] $0 to < $10 million
[11] $10 million to < $20 million

6.72 The net cost to the PBS of tafamidis was $20 million to < $30 million in Year 1, increasing to $30 million to < $40 million in Year 6, a total of $200 million to < $300 million over 6 years. With revised prices for year 4+ in the pre-PBAC response the year 6 cost was reduced to $20 million to < $30 million, a total of $200 million to < $300 million over 6 years.

6.73 The estimated utilisation and cost of tafamidis to the PBS/RPBS is uncertain, and likely to be underestimated, due to the following issues:

- The prevalence of ATTR-CM was estimated using the same sources and methodology previously considered by the PBAC to be underestimated (paras 6.75, 7.12-7.13, Tafamidis PSD, March 2021 meeting).
- The diagnostic rates of ATTR-CM and ATTR-CM with NYHA class I-II heart failure in the Australian setting and uptake of tafamidis in the eligible population were assumed and remain uncertain.

- The resubmission calculated the incident and prevalent populations treated with tafamidis from the estimated overall prevalent population derived from the epidemiological analysis which would incorporate mortality over time, but inappropriately removed patients who had died from the eligible prevalent pool. The incident and prevalent populations treated with tafamidis were therefore underestimated.
- The calculated proportions of patients with persistent NYHA class III heart failure may not be reasonable, given the lack of longitudinal data for persistence of heart failure symptoms. In addition, aggregation of patients transitioning to NYHA class III and IV most likely overestimated the discontinuation of tafamidis due to disease progression.

6.74 In March 2021, the PBAC had considered the methodology underestimated the PBS impact, but considered that the approach was appropriate in the context of these estimates being used to implement an RSA, and given the lack of more reliable alternative data on which to base the estimates (para 7.12, Tafamidis PSD, March 2021 meeting). In September 2021, the PBAC had considered that the patient population (i.e. patient numbers derived based on patients with NHYA class I, II and non-persistent class III heart failure) may form a reasonable basis for the RSA expenditure caps, given that the Committee had previously considered that the efficacy was uncertain in patients with NYHA class III failure (para 10.03, Tafamidis PSD, September 2021 meeting). At the same time, PBAC remained of the view that a future resubmission should outline an RSA to provide more certainty with respect to the total cost, and to manage the risk associated with use in a broader population in which cost-effectiveness is unknown (para 10.4, Tafamidis PSD, September 2021).

6.75 The ESC considered that diagnosis of ATTR-CM is occurring earlier than previously and rates of diagnosis may increase further. In addition, there is a high level of awareness of tafamidis for clinicians and consumers, which is likely to drive rapid uptake if listed on the PBS.

6.76 The pre-PBAC response agreed that there is inherent cumulative uncertainty in the estimated utilisation, and stated that a volume-based risk share agreement is proposed to manage the risk of use in a broader population.

Quality Use of Medicines

6.77 The resubmission proposed providing education for treating clinicians on the approved restriction, to ensure that tafamidis is prescribed according to the initiation and discontinuation criteria as per the continuation restriction. In addition, the resubmission proposed a training program for general practitioners and specialists, patient and carer resource materials and post marketing surveillance including a risk management plan.

Financial Management – Risk Sharing Arrangements

6.78 The resubmission proposed a risk sharing arrangement to manage the risk associated with use in a broader population where tafamidis has not been demonstrated to be cost-effective and to reduce the risk of use beyond the stopping rule (i.e. progression to persistent NYHA class III or NYHA class IV heart failure). The proposed caps were at 100% of estimated expenditure in Years 1-3 of listing and at 105% of estimated expenditure in Years 4-6 of listing. The proposed rebates were [redacted]% for use above the caps in Years 1-3 and [redacted]% for Years 4-6.

6.79 The resubmission and pre-PBAC response argued that the higher cap (105%) and lower rebate ([redacted]%) proposed for Years 4-6 of listing appropriately accounts for uncertainty in diagnosis rates and uptake of tafamidis over the later years, given tafamidis is a first-in-field disease modifying medicine for the treatment of ATTR-CM, and is consistent with the upper limit of diagnosis observed in the sensitivity analysis.

6.80 The PBAC recalled it previously considered that expenditure caps higher than the resubmission's estimated financial expenditure would not adequately manage the risk associated with use in a broader population (para 10.1, Tafamidis PSD, March 2021 PBAC meeting with September 2021 Addendum). The ESC considered the proposed 105% cap with [redacted]% rebate for years 4-6 would not adequately address the risks associated with use in the broader population or beyond the intended eligible population in those years.

Table 13: Proposed risk sharing arrangement caps based on estimated utilisation of tafamidis

	Year 1 (2024)	Year 2 (2025)	Year 3 (2026)	Year 4 (2027)	Year 5 (2028)	Year 6 (2029)
Proposed caps at estimated expenditure (100%)	$[redacted][1]	$[redacted][3]	$[redacted][4]	-	-	-
Proposed caps above estimated expenditure (105%, pre-PBAC proposed)	-	-	-	$[redacted][3]	$[redacted][2]	$[redacted][1]
Proposed rebate (%)	[redacted]					

Source: Table 4.6.3, p277 of the resubmission.

The redacted values correspond to the following ranges:

[1] *$20 million to < $30 million*

[2] *$30 million to < $40 million*

[3] *$40 million to < $50 million*

[4] *$50 million to < $60 million*

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of tafamidis for patients with transthyretin amyloid cardiomyopathy, with NHYA class I-II heart failure. The PBAC considered that there was a clear clinical benefit for tafamidis, including a reduction in mortality. The PBAC considered that the ICER was high, but would be acceptable at the lower price proposed in the pre-PBAC response, in the context of the high unmet need for this patient population. The PBAC considered that a risk sharing arrangement would be

required due to a high risk of utilisation outside the proposed restriction and to address uncertainty around the overall financial impact.

7.2 The PBAC acknowledged the consumer comments in continued support of listing tafamidis, and recognised the ongoing impact that a lack of PBS therapies for this condition was having on patients' prognosis and quality of life.

7.3 The PBAC recalled it previously considered that the resubmission's proposal for tafamidis to be discontinued in patients with persistent class III heart failure may be difficult to implement in practice given the subjective nature of NYHA classification and would likely result in use outside the restriction (para 10.2, tafamidis PSD, March 2021 PBAC meeting with September 2021 addendum). The PBAC acknowledged the clinical expert advice that discontinuation of patients with NYHA class III heart failure could be managed in practice. The PBAC considered that it would be appropriate to include this in the restrictions, though there remained substantial risk of use outside of the restriction in patients commenced on tafamidis who had progressed, but where the patient and the clinician were unwilling to stop the medication in case tafamidis was slowing disease progression.

7.4 The PBAC recalled that it had previously accepted the clinical claim that tafamidis is superior in efficacy compared with standard management, and although a moderate amount of uncertainty remained, it had previously recognised that tafamidis provided a substantial and clinically relevant improvement in efficacy overall. The PBAC considered that limiting eligibility to patients with NYHA class I or II heart failure on initiation addressed some uncertainty regarding the magnitude of benefit for the Australian PBS population. The PBAC also considered that the post hoc analyses of the ATTR-ACT and B3461045 long term extension data (updated August 2021 data cut) were supportive of a survival benefit for tafamidis, with a statistically significant reduction in all-cause mortality for patients with baseline NYHA class I/II in the tafamidis 80/61 mg treatment arm compared to the placebo/tafamidis arm (HR: 0.502; 95% CI: 0.346, 0.727).

7.5 The PBAC also recalled its previous concern that results for key outcomes were similar for the 20 mg and 80 mg doses of tafamidis and that adequate justification for the 80 mg dose rather than the 20 mg had not been provided (paragraphs 7.9 and 7.10, tafamidis PSD, July 2020). The PBAC noted that longer-term data from the extension study provided in the submission appeared to support a small increase in efficacy with the tafamidis meglumine 80 mg dose over the 20 mg dose.

7.6 The PBAC recalled that it had previously accepted the claim of inferior safety compared with standard management (paragraph 7.9, tafamidis PSD, March 2021 PBAC meeting). The PBAC noted that there remained no significant toxicity or safety signals with tafamidis in the trial, though the safety data for tafamidis were still based on relatively few patients.

7.7 The PBAC recalled it previously advised that an ICER of $80,000 per QALY gained for the model applying the two sensitivity analyses in the March 2021 pre-PBAC response

would be acceptable. The PBAC noted that the requested changes had been applied in the resubmission's economic model, along with application of discontinuation of patients with persistent NYHA class III heart failure. However, the PBAC considered there remained some uncertainty regarding the modelled outcomes; for example, the model base case continues to maintain an ongoing treatment benefit on cardiovascular hospitalisations and heart failure disease progression after tafamidis treatment-related discontinuation.

7.8 At the prices proposed in the pre-PBAC response ($[redacted] in years 1-3 and $[redacted] in subsequent years) the corrected ICER was $115,000 to < $135,000 per QALY gained. The PBAC considered that at a DPMQ of $[redacted] (the year 1-3 proposed price) the ICER of $135,000 to < $155,000 per QALY was unacceptably high and uncertain. Notwithstanding the remaining uncertainty in the modelled cost-effectiveness estimates, the PBAC considered that tafamidis would be acceptably cost-effective based on a cost no higher than a DPMQ of $[redacted] (ICER of approximately $95,000 to < $115,000 per QALY), the price proposed in the pre-PBAC response for years 4-6. This was in the context of a high unmet clinical need in a relatively small patient population, with financial caps to mitigate the risk to the Commonwealth of use in a broader population.

7.9 The PBAC recalled it had previously considered that the patient population (i.e. patient numbers derived based on patients with NHYA class I, II and non-persistent class III heart failure) may form a reasonable basis for the RSA expenditure caps (para 10.3, tafamidis PSD, September 2021 PBAC meeting). The PBAC considered that there remains considerable uncertainty regarding the rate of diagnosis, uptake and continuation of tafamidis, noting that there is a high level of awareness of tafamidis for clinicians and consumers, which is likely to drive rapid uptake if listed on the PBS.

7.10 The PBAC remained of the view that an RSA would be required to provide more certainty with respect to the total cost, and to manage the risk associated with use in a broader population and potential continuation in patients progressing to NYHA class III heart failure, in which cost-effectiveness is unknown (para 10.4, tafamidis PSD, September 2021 PBAC meeting). The PBAC considered the submission's proposal for caps to be based above the financial estimates (at 105%) with a [redacted]% rebate for years 4-6 did not appropriately mitigate risk to government, and would not adequately address the risks associated with use in the broader population or beyond the intended eligible population in those years. The PBAC considered that financial caps for the RSA should be based at no higher than the levels of estimated expenditure, with a 100% rebate for expenditure above the caps.

7.11 The PBAC recommended that the Early Supply Rule should apply.

7.12 The PBAC found that the criteria prescribed by the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022 for Pricing Pathway A were met. Specifically, the PBAC found that in the circumstances of its recommendation tafamidis:

a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy compared with standard management in terms of survival and cardiovascular-related hospitalisations;

b) The treatment is expected to address a high and urgent unmet clinical need as there are no effective alternative treatments for this patient population;

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.13 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new medicinal product as follows:

Category / Program: GENERAL – General Schedule (Code GE)					
MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
TAFAMIDIS					
tafamidis 61 mg capsule, 30	NEW MP	1	30	5	Vyndamax
					Early supply rule applies? Yes
Common 'Notes' applying to all attached restriction summaries:					
7606	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.				
7607	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.				
7608	**Administrative Advice:** Special Pricing Arrangements apply.				
Restriction Summary [new 1] / Authority Required					
	Indication: Transthyretin amyloid cardiomyopathy				
	Treatment Phase: First PBS-subsidised prescription for this drug				
	Clinical criteria:				
	The treatment must be for wild-type transthyretin-mediated amyloid cardiomyopathy, with documented evidence of transthyretin precursor protein present; or				
	The treatment must be for variant transthyretin-mediated (also known as hereditary transthyretin-mediated) amyloid cardiomyopathy, with documented evidence of transthyretin precursor protein present				
	AND				
	Clinical criteria:				
	Patient must have experienced at least one episode of hospitalisation that was a direct result of heart failure; or				
	Patient must have clinical evidence of heart failure without hospitalisation that required treatment with a diuretic for improvement				
	AND				

	Clinical criteria:
	Patient must have/have had New York Heart Association class I heart failure at the time of commencing this drug; or
	Patient must have/have had New York Heart Association class II heart failure at the time of commencing this drug
	AND
	Clinical criteria:
	Patient must have an end-diastolic interventricular septal wall thickness of at least 12 mm on imaging
	AND
	Clinical criteria:
	Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 ml/minute/1.73 m^2
	Treatment criteria:
	Must be treated by a medical practitioner who is any of the following: (i) a cardiologist, (ii) a consultant physician with experience in the management of amyloid disorders; this authority application must be sought by the same medical practitioner providing treatment
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	Prescribing Instructions: Evidence of clinical findings to establish the diagnosis: In this authority application, confirm that there is documented evidence of transthyretin precursor protein through either (1) alone, or, both (2) and (3), from the list below: Confirm the following has been completed: (1) amyloid expert centre histology findings derived via immunohistochemistry or mass spectrometry; OR (2) bone scintigraphy with grade 2-3 finding AND (3) Confirm that there are negative results for monoclonal protein on each of the following three tests: (a) serum immunofixation (also known as protein electrophoresis) (b) urine immunofixation (c) serum free light chains blood test State which of (1) to (3) above has been completed, as well as the: • date of the finding, • imaging/pathology report number/code that links the finding to the patient, • name of the amyloid expert centre in this authority application. For end-diastolic interventricular septal wall thickness (at least 12 mm), confirm that: • imaging (echocardiogram or magnetic resonance imaging) has been undertaken; and • that the imaging report is stored in the patient's medical records. State the date that the imaging was performed and the thickness (in mm) in this authority application.
	Prescribing Instructions: Where this authority application is to transition a patient from non-PBS subsidised to PBS-subsidised supply (i.e. a 'grandfathered' patient), confirm the following: (i) the patient's heart failure has not worsened to persistent New York Heart Association Class III/IV heart failure while taking this drug.
	Administrative Advice:

	Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Administrative Advice: The Australian Amyloid Network provides a list of clinic centres that manage amyloidosis. It also provides a list of Australian anatomical pathology laboratories to be contacted for tissue review and immunohistochemistry for amyloid typing. For the purposes of this restriction, these providers are considered to be amyloid expert centres.
Restriction Summary [new 2] / Treatment of Concept: [new 2.1]: Authority Required	
	Indication: Transthyretin amyloid cardiomyopathy
	Treatment Phase: Second and subsequent PBS-subsidised prescriptions for this drug
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition,
	AND
	Clinical criteria:
	Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 ml/minute/1.73 m^2
	AND
	Clinical criteria:
	The treatment must be ceased where the patient's heart failure has worsened to persistent New York Heart Association (NYHA) Class III/IV heart failure.
	AND
	Clinical criteria:
	The treatment must be ceased where the patient has received any of: (i) a heart transplant, (ii) a liver transplant, (iii) an implanted ventricular assist device.
	Treatment criteria:
	Must be treated by a medical practitioner who is any of the following: (i) a cardiologist, (ii) a consultant physician with experience in the management of amyloid disorders; this authority application must be sought by the same medical practitioner providing treatment.
	Prescribing Instructions: Confirm whether heart failure has worsened to NYHA Class III/IV since the last authority application (yes/no). If 'no', continued PBS-subsidy is available. If 'yes', continued PBS-subsidy is available, but the prescriber must undertake a review of the patient within 3 months to determine whether the worsening heart failure was transient or persistent. Prescribe no more than 2 repeat prescriptions in such an instance.

	Where this subsequent clinical review finds that the heart failure persists as NYHA Class III/IV heart failure despite active treatment with this drug, then PBS-subsidy is not available.
	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 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 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.

10 Sponsor's Comment

Pfizer welcomes the PBAC's recommendation for PBS-listing of tafamidis for the treatment of transthyretin amyloid cardiomyopathy and looks forward to making this treatment available for patients with this debilitating and life-threatening condition.