An addendum to these minutes has been included at the end of the document.

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

1 Purpose of submission

1.1 The resubmission requested an Authority Required (written) listing for tafamidis for the treatment of patients with transthyretin cardiac amyloidosis (ATTR-CM). The PBAC previously considered tafamidis for ATTR-CM at the July 2020 PBAC meeting.

1.2 Listing was requested on the basis of a cost effectiveness analysis versus standard management of ATTR-CM (best supportive care).

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Patients with wild-type or variant transthyretin cardiac amyloidosis with end-diastolic interventricular septal wall thickness of at least 12 mm, with NYHA class I-II. Patients with NYHA class III who return to NYHA class II with adequate management e.g. diuretics are permitted to initiate treatment while patients with persistent NYHA class III are excluded.
Intervention	Tafamidis 61 mg capsule, once daily.
Comparator	Standard heart failure management (e.g. diuretics and antiarrhythmic medicines).
Outcomes	Mortality, cardiovascular-related hospitalisations, functional measures (6 Minute Walk Test), quality of life (KCCQ-OS score, EQ-5D-3L).
Clinical claim	Tafamidis has superior efficacy and inferior safety compared to standard heart failure management.

Source: Table 1.1.1, p.4 of the resubmission.
Abbreviations: NYHA, New York Heart Association.
Underlined text indicates changes compared to the previous submission.

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, p.58).

2.3 The recommended dose in the approved Product Information (PI) is 61 mg once daily, with the PI noting this is bioequivalent to 80 mg tafamidis meglumine, which can be administered as four 20 mg capsules.

2.4 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

2.5 Table 2 summarises the key matters of concern from the July 2020 submission for tafamidis.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed it
Context and intended use		
Proposed PBS listing	The PBAC considered the requested restriction should more closely align with the ATTR-ACT trial inclusion and exclusion criteria, requiring evidence or history of heart failure, NYHA class I to III, an end-diastolic interventricular septal wall thickness ≥12 mm, and excluding patients with eGFR <25 mL/min/1.73 m^2 (para 7.3).	The proposed restriction was amended to align with the ATTR-ACT trial inclusion and exclusion criteria, with two exceptions: (i) consultant physicians with experience in amyloid disorders are retained in addition to specialist cardiologists, for patient management; and (ii) eligibility is limited to patients with NYHA class I and II heart failure on initiation only. Patients with NYHA class III heart failure who return to NYHA class II with adequate management may initiate tafamidis but patients with persistent NYHA class III are ineligible, and patients progressing to NYHA stage III may continue tafamidis.
	The PBAC considered that patients should discontinue tafamidis if they progress to NYHA class IV, or receive a heart or liver transplant or an implanted cardiac ventricular assist device (para 7.3).	The requested restriction was amended to exclude these patients.
Bone scintigraphy	The PBAC noted that data supporting use of bone scintigraphy were based on use in a specialised amyloid centre, and considered that the positive predictive value may not be reproduced in non-specialised centres given interpretation of bone scans is potentially subjective, and considered that data regarding the positive predicted value of bone scintigraphy in non-specialised centres (as part of the diagnostic algorithm proposed by the submission) would be informative (para 7.4).	The resubmission presented expert opinion from a leading Australian nuclear medicine specialist that scans are able to be performed by all centres, and that reporting is now performed with standard criteria from consensus guidelines in Dorbala et al, 2019.

Component	Matter of concern	How the resubmission addressed it
Tafamidis dose strength	The PBAC noted 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 (para 7.10).	The resubmission noted that the ATTR-ACT trial was not powered to evaluate differences between tafamidis dose strengths. In addition, the resubmission presented a comparison of the 80 mg and 20 mg dose strengths using a post hoc subgroup analysis of the combined ATTR-ACT and B3461045 data sets.
Clinical evaluation		
Clinical claim in efficacy	The PBAC accepted the clinical claim of superiority versus standard management, but was concerned that the magnitude of benefit of tafamidis was uncertain as NYHA class may be a treatment effect modifier and: • In patients with baseline NYHA class III heart failure, tafamidis was associated with an increase in hospitalisations and an uncertain impact on survival (para 7.9). • It was unclear whether the distribution of NYHA classes from the ATTR-ACT trial will be applicable to the Australian setting (para 7.9). • It was unclear whether newly diagnosed patients would have more benign clinical courses and that the overall natural history of ATTR-CM may evolve with the changing diagnostic paradigm (para 7.9).	• The clinical claim was amended to exclude initiation of tafamidis in patients with persistent NYHA class III heart failure. • The resubmission presented further comparisons of the ATTR-ACT population and the Australian setting and claimed that more recently diagnosed Australian patients will be more closely aligned to the ATTR-ACT population in terms of baseline NYHA class. • The resubmission presented additional studies of the natural history of ATTR-CM and claimed that earlier diagnosis delays disease progression.
Clinical claim in safety	The PBAC considered that the claim of non-inferior safety versus standard management was possibly reasonable, but that the clinical safety dataset was small and inadequate to make a claim of non-inferior safety (para 7.11).	The clinical claim was amended to inferior safety versus standard management.
Economic evaluation		
Structure of the economic model	The PBAC considered that the model structure did not form a reliable basis for decision making (para 7.12): • Patients were assumed to remain in the same NYHA class over the duration of the model which did not reflect the progressive nature of ATTR-CM.	• The new model structure allowed patients to progress and regress between NYHA class categories (NYHA I/II, NYHA III/IV).

Component	Matter of concern	How the resubmission addressed it
	• A constant probability of hospitalisation was applied over the duration of the model, which was inappropriate as CV hospitalisations would be expected to increase with age.	• In the new model, CV hospitalisations were included as a health state (previously included as an event). Patients could transition between recent and no recent CV hospitalisation states. Constant probabilities of hospitalisation were used in the model from 2.5 years. The number of hospitalisations per hospitalised patient, assumed to be constant over time, was captured to cost CV hospitalisation events.
	• The implicit assumption that all CV hospitalisations would be non-fatal was inappropriate as trial data indicated both fatal and non-fatal hospitalisation events.	• Individual patient data from the ATTR-ACT trial (subgroup with NYHA class I/II at baseline) were used to derive transition probabilities for movement between NYHA class I/II and III/IV, CV-related hospitalisations, and death.
	• The implicit assumption that the treatment effect is maintained following treatment discontinuation was inappropriate as increasing proportions of patients discontinue over time and spend longer durations without therapy (not accruing drug costs, but deriving treatment benefit).	• Not addressed in the resubmission. Treatment discontinuation rates were applied to drug costs only, with no impact on survival, NYHA class, or CV hospitalisations.
Survival extrapolation	Different parametric functions for overall survival were applied to the tafamidis and best supportive care arms. The PBAC considered that it would be more appropriate to apply the same function to both arms (para 7.13).	The revised model no longer used parametric functions to estimate survival.
Applicability of the modelled population	The PBAC considered that there were substantial differences in modelled incremental benefits associated with tafamidis treatment in patients with NYHA class I/II and those with NYHA class III heart failure. It was unclear whether the distribution of NYHA classes from the ATTR-ACT trial would be applicable to the Australian setting (para 7.15).	The revised proposed PBS population excluded patients with persistent NYHA class III symptoms. Participants in the ATTR-ACT trial with NYHA class III at baseline were excluded from the revised model.
Cost-effectiveness estimates	The model generated an ICER of more than $200,000 per QALY gained which was considered unacceptably high. The PBAC stated that a significantly lower and more certain ICER would be required (para 7.15).	The resubmission proposed a lower effective DPMQ ($[redacted]; a 58.7% reduction compared to the previous submission), which reduced the ICER to $[redacted][1] per QALY gained (corrected for various errors during the evaluation).
Predicted use in practice		
Financial estimates	The PBAC considered that further work was required to determine the size of the eligible population in Australia, particularly the incidence and prevalence of the condition and that more reliable financial estimates would be required to inform a RSA (para 7.17, 7.18).	The resubmission presented a revised utilisation and cost model, with new data sources used to inform prevalence, diagnosis and uptake rates.

Source: Tafamidis Public Summary Document, July 2020 PBAC meeting, and Overview, pp. xiii-xiv, xvii-xviii of the resubmission.

Abbreviations: ATTR-CM, transthyretin amyloid cardiomyopathy; CV, cardiovascular, eGFR, estimated glomerular filtration rate; ICER, incremental cost effectiveness ratio; NYHA, New York Heart Association; QALY, quality adjusted life year; RSA, risk share arrangement.
The redacted value corresponds to the following range:
[1]$155,000 to < $255,000/QALY gained

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

3 Requested listing

3.1 The requested listing is presented below. The Secretariat proposed only minor formatting changes, and the addition of administrative notes stating that Special Pricing Arrangements apply, and that no increase in the maximum quantity or number of repeats would be authorised (not shown below).

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

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	Medical Practitioners
Condition:	Transthyretin amyloid cardiomyopathy
PBS Indication:	Transthyretin amyloid cardiomyopathy
Treatment phase:	Initial
Restriction:	Authority Required - In Writing
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
Clinical criteria:	The condition must be wild-type transthyretin amyloidosis; or The condition must be variant transthyretin type amyloidosis Patient must have evidence or history of heart failure AND Patient must have New York Heart Association class I to II heart failure including patients who are returned to NYHA class II with adequate management e.g. diuretics. Patients must not have persistent NYHA class III heart failure. AND The condition must have an end-diastolic interventricular septal wall thickness of at least 12 mm 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. Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 ml/minute/1.73m^2

Prescriber 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 Persistent NYHA class III is heart failure which is not returned to NYHA class II despite adequate management e.g. diuretics after 3-6 months

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	Medical Practitioners
Condition:	Transthyretin amyloid cardiomyopathy
PBS Indication:	Transthyretin amyloid cardiomyopathy
Treatment phase:	Continuing
Restriction:	Authority Required - In Writing
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
Clinical criteria:	Patient must have previously received PBS-subsidised treatment with this drug for this condition Patient must have an estimated glomerular filtration rate (eGFR) greater than 25 ml/minute/1.73m^2 Patient must have New York Heart Association class I to III heart failure
Prescriber Instructions:	The treatment must be ceased if any of the following occur: (i) Patient progresses to New York Heart Association class IV heart failure, or (ii) Patient receives a heart / liver transplant, or an implanted cardiac ventricular assist device

Source: Tables 1.4.2-1.4.3, pp.35-37 of the resubmission.

3.2 The resubmission proposed a lower effective DPMQ than the previous submission ($[redacted]; a 58.7% reduction compared to the previous submission), and a special pricing arrangement with a [redacted]% rebate on the published DPMQ per script.

3.3 The proposed listing was for the tafamidis 61 mg free acid formulation (bioequivalent to tafamidis meglumine 80 mg). Consistent with the previous submission, the sponsor did not request listing of the tafamidis meglumine 20 mg formulation.

3.4 The requested restriction was narrower than the registered TGA indication, which is broadly for hereditary or wild-type ATTR-CM.

3.5 The resubmission noted the PBAC's previous concerns that the magnitude of benefit of tafamidis was uncertain in patients with baseline NYHA class III heart failure, and that tafamidis was associated with an increase in hospitalisations and an uncertain impact on survival in these patients (para 7.9, tafamidis Public Summary Document (PSD), July 2020 PBAC meeting). Therefore, the resubmission proposed that patients with non-persistent NYHA class III heart failure may be eligible to initiate PBS listed tafamidis if their heart failure transitions to NYHA class II with appropriate treatment (e.g. diuretics), but patients with persistent NYHA class III heart failure (i.e. heart

failure which is not returned to NYHA class II despite adequate management after 3-6 months) are ineligible.

3.6 The requested restriction for continuing treatment included patients who progress to NYHA class III heart failure after initiation of tafamidis.

3.7 The PBAC noted that the proportions of patients with persistent NYHA class III heart failure (i.e. not eligible for initiation of PBS subsidised tafamidis), in the Australian population is not known. The submission claimed that, based on the ATTR-ACT trial, only 20% of patients with NYHA class III heart failure at the time of diagnosis are likely to improve to class II (and hence become eligible for tafamidis), although the Pre-Sub-Committee Response (PSCR) noted that clinical experts consulted indicated that this may be as high as 50%.

3.8 The restriction for continuing treatment included two discontinuation criteria: (i) progression to NYHA class IV heart failure; and (ii) heart/liver transplant, or implanted cardiac ventricular assist device.

3.9 The resubmission assumed that 300 patients would be grandfathered onto the PBS. These numbers were unconfirmed, and no restriction wording was proposed.

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

4 Population and disease

4.1 ATTR-CM is a rare, late onset, progressive disease, characterised by extracellular deposition of misfolded transthyretin (TTR) amyloid fibrils in the cardiac atrial and ventricular walls, and/or direct amyloid proteotoxicity (Siddiqi et al. 2018). Amyloid fibril deposition results in progressive 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.

4.2 ATTR-CM is related to either a wild TTR genotype (ATTRwt; most common), or an autosomal dominant, inherited or variant TTR genotype (ATTRm), and is most prevalent in males ≥ 60 years of age, with prevalence increasing with age (Siddiqi et al. 2018). Disease trajectory is heterogeneous between TTR genotypes in terms of organ involvement, age of onset, presentation and prognosis, and the ATTRm genotype also varies between mutations in terms of prevalence, pattern of organ involvement, prognosis, race and region.

4.3 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, glaucoma (Siddiqi et al. 2018). However, diagnosis of ATTR-CM in current clinical practice 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 ATTRm and 3.5 years for ATTRwt, with death most likely due to cardiovascular (CV) causes (cardiac arrhythmia, fulminant heart failure; Dungu et al. 2012; Maurer et al. 2017; Ruberg et al. 2012).

4.4 The current and proposed clinical management algorithms were the same as presented in the previous submission, with the addition of 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 positioned 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, histological confirmation of transthyretin precursor protein in cardiac tissue, and immunochemistry or mass spectrometry as required, with or without gene testing.

4.5 At the July 2020 meeting, the PBAC noted that the data supporting the use of bone scintigraphy were based on use in a specialised amyloid centre, and considered that the positive predictive value may not be reproduced in non-specialised centres given that interpretation of bone scans is potentially subjective. In addition, the PBAC noted the potential for inconsistency in bone scintigraphy reporting, especially by facilities with little prior experience or expertise in reporting studies for the diagnosis of ATTR-CM (para 7.4-7.5, Tafamidis PSD, July 2020 PBAC meeting).

4.6 The PBAC noted that the resubmission presented expert opinion from a leading Australian nuclear medicine specialist that bone scintigraphy scans are able to be performed by all centres, and that reporting is now performed with standard criteria from consensus guidelines in Dorbala et al, 2019.

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

5 Comparator

5.1 The resubmission nominated standard management of the symptoms of ATTR-CM (diuretic and/or antiarrhythmic medicines) as the main comparator. At the July 2020 meeting, the PBAC considered that standard management of ATTR-CM was the appropriate comparator (para, 7.7, Tafamidis PSD, July 2020 PBAC meeting).

For more detail on the 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 natural history of the disease, and highlighted the lack of effective therapies available for this condition. The clinician considered that ATTR-CM patients seen in Australia broadly

reflect the population included in the ATTR-ACT trial, and noted that there has been an increasing awareness of the condition, resulting in earlier diagnoses. The clinician also estimated that approximately 50% of patients diagnosed as NYHA class III would go on to improve to class II, as patients frequently arrive in clinics on inappropriate medications and diet, and improvements are seen once these are corrected. The clinician emphasised that tafamidis was a highly tolerable once-a-day oral treatment, easily managed by patients. The PBAC considered that the hearing was informative as it provided a clinical perspective on treating this uncommon disease.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (11) and health care professionals (2) via the Consumer Comments facility on the PBS website. The comments described the debilitating symptoms of ATTR-CM and the disease's impact on the quality of life of both patients and their families. The comments highlighted the challenges of timely diagnosis, the lack of available therapies, and the difficulties in accessing privately funded tafamidis. Individuals who had used tafamidis described a range of benefits of treatment including slowing down disease progression and supporting them to continue with normal day-to-day activities. The PBAC noted the advice received from a cardiologist with experience managing patients with ATTR-CM that an increasing number of patients with this condition were being referred to specialist clinics.

Clinical trials

6.3 The submission was based on one randomised placebo controlled trial (ATTR-ACT) considered in the previous submission, comparing tafamidis meglumine in combination with standard management to standard management alone, in patients with transthyretin amyloid cardiomyopathy with evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness ≥ 12 mm, and interim results from the ongoing long term extension safety study B3461045, considered in the previous submission.

6.4 In addition, the resubmission presented new post hoc subgroup analyses of the ATTR-ACT trial, further interim results from the ongoing long term extension study B3461045, and post hoc subgroup analyses of the combined ATTR-ACT and B3461045 data sets. Safety outcomes were unchanged from the July 2020 submission. Treatment emergent adverse events reported in the ongoing B3461045 long term extension study were not presented.

Table 3: Trials and studies presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
ATTR-ACT (B3461028) (NCT01994889)	A multicentre, international, phase 3, double-blind, placebo-controlled, 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.
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(Supplement 1, October 2019), 1169.

Source: Table 2.2.1, pp.47-49 of the resubmission.

6.5 The key features of the studies are summarised in the table below.

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)	R, DB, PC, MC, 30 months	Unclear	18-90 years, ATTR-CM with CV involvement[b]	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)[c]	Broad Cohort Tafamidis 20/61 mg (N=116)[e] Tafamidis 80/61 mg (N=230)[e]	51 months[a] (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; DB, double blind; EQ-5D, European quality of life 5 dimension questionnaire; IPD, individual patient data; KCCQ, Kansas City Cardiomyopathy Questionnaire; MC, multi-centre; NK, not known; NR, not reported; PC, placebo controlled; R, randomised.

[a] ATTR-ACT treatment phase duration and extension study duration.

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

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

[d] Cohort B was excluded from the resubmission.

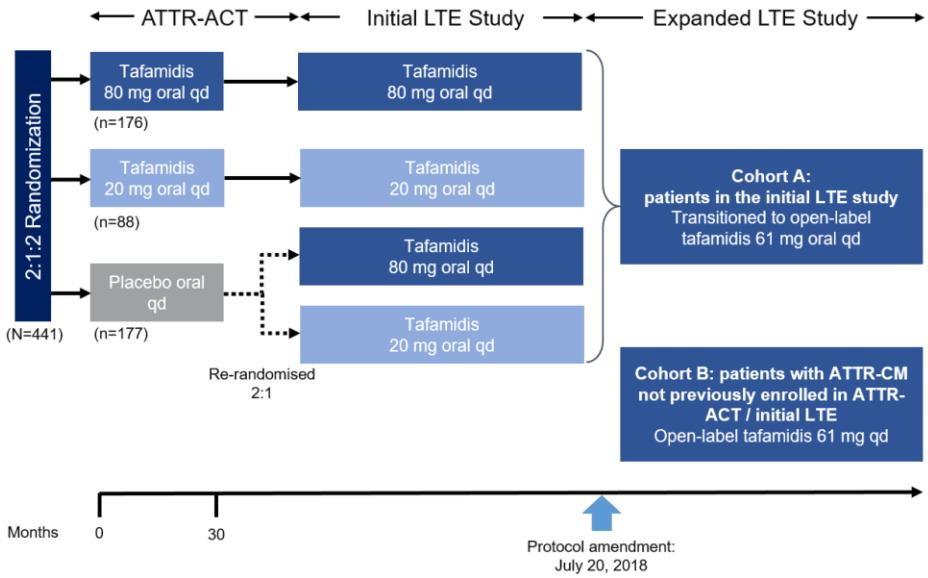
[e] Includes patients switching from placebo.

6.6 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 arms, compared to the placebo arm, may have biased trial outcomes in favour of tafamidis (para 6.10, Tafamidis PSD, July 2020 PBAC meeting).

6.7 Differences in baseline risk and disease severity between treatment arms in the ATTR-ACT trial were not adequately explained in the resubmission. The PSCR argued that the baseline difference in proportions of patients with NYHA Class III did not bias outcomes in favour of tafamidis because this had been taken into account in statistical analyses. Use of the Finkelstein-Schoenfeld methodology stratified by NYHA class and TTR genotype, and inclusion of NYHA class and TTR genotype as a covariates in statistical models, may not have addressed differences between treatment arms in terms of other known (e.g. NT-proBNP) and unknown prognostic factors. The impact of differences between treatments arms on the results of the ATTR-ACT trial remained unclear.

6.8 As shown in the figure below, 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.

Figure 1: ATTR-ACT and B3461045 long term extension study design



Source: Figure 2.3.1, p.53 of the resubmission; Figure 3 of the PSCR.
Abbreviations: ATTR-CM, cardiac transthyretin amyloidosis; LTE, long term extension; qd, once daily.

6.9 The flow of patients from the ATTR-ACT trial through the B3461045 extension study was poorly documented. The proportions of patients continuing or initiating tafamidis in each of the tafamidis 20/61 mg and 80/61 mg treatment arms, as well as the tafamidis dose intensity, exposure and duration of treatment by dose, was not adequately reported, particularly for patients switching from placebo to tafamidis.

The PSCR clarified the allocation to treatment arms for continuing patients, although demographic and disease data by prior tafamidis or placebo treatment, discontinuations, duration of treatment exposure and dose intensity were not presented. Reporting of outcomes was not pre-specified and was ad-hoc in terms of time intervals and outcomes reported. The risk of bias in the B3461045 study was high.

6.10 At the July 2020 meeting the PBAC considered that it was unclear whether the distribution of NYHA classes from the ATTR-ACT trial will be applicable to the Australian setting, particularly as changes in the diagnostic algorithm will likely affect the distribution of NYHA classes among patients with ATTR-CM. The July 2020 pre-PBAC response argued that earlier diagnosis will better align the eligible Australian population with the ATTR-ACT trial, but the PBAC considered that it was unclear whether newly diagnosed patients would have more benign clinical courses and that the overall natural history of ATTR-CM may evolve with changing diagnostic paradigms.

6.11 To inform the applicability of the ATTR-ACT trial to the Australian setting, the resubmission presented a comparison of the ATTR-ACT trial population to two Australian ATTR-CM study abstracts previously considered at the July 2020 PBAC meeting (Burrage et al. 2017; Lasica et al. 2018), and Choi et al. 2020 (an update of Lasica et al. 2018). In addition, the resubmission presented data from the B3461045 Cohort B, not previously considered by the PBAC (Australian subgroup, N=32). The resubmission acknowledged that all these studies excluded patients with the ATTRm genotype, but argued that if the Australian studies had included patients with ATTRm, the populations would be similar to the Australian setting. Only sparse demographic and disease characteristics of patients included in Cohort B of the B3461045 study were reported and it was unclear whether this population would be eligible for PBS-subsidised tafamidis under the requested restriction. The PSCR presented demographic and disease data for Cohort A. However, the proportion of patients enrolled in Cohort B of the extension study who would be eligible under the proposed restriction was not addressed.

6.12 As with the July 2020 submission, there were limited data available to assess the applicability of the ATTR-ACT trial to the Australian setting. This was not unexpected given the relative rarity of ATTR-CM. However, age, NYHA class, TTR genotype and ATTRm mutation phenotype have been identified as baseline prognostic indicators for ATTR-CM and may therefore affect baseline risk. Any differences between the ATTR-ACT trial and the Australian setting in these indicators may therefore result in differences in the absolute benefit of tafamidis.

6.13 The resubmission presented Australian data from Choi et al. 2020 and selected international studies (Connors et al. 2016, Grogan et al. 2016; Lane et al. 2019; Law et al. 2020; Staron et al. 2019; Nativi-Nicolau et al. 2020) to address the PBAC's previous concerns regarding the potential for the natural history of ATTR-CM to evolve with changing diagnostic paradigms. The studies suggested the availability of non-invasive

diagnostic tests (scintigraphy) and an effective disease modifying treatment option has substantially increased the incidence of ATTR-CM diagnoses in the international and Australian settings. The importance of earlier diagnosis and treatment of ATTR-CM was emphasised in all studies, but the resubmission's claim that earlier diagnosis and treatment would result in improvements in survival was unsupported.

Comparative effectiveness

ATTR-ACT trial results

6.14 The results of the ATTR-ACT trial, presented in the July 2020 submission, are reproduced below.

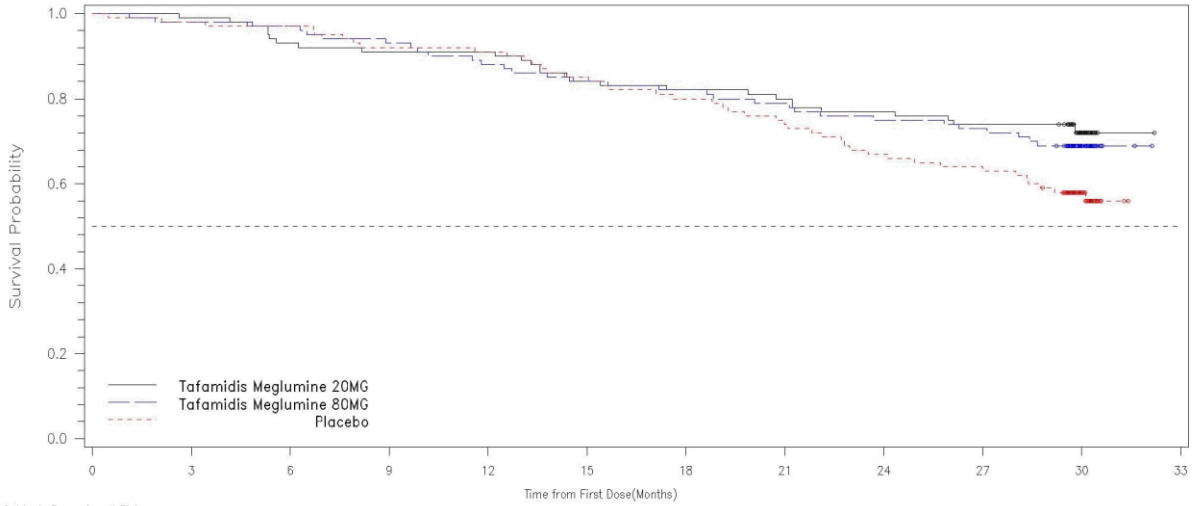
6.15 Table 5 summarises time to all-cause mortality by tafamidis dose for the ATTR-ACT trial at 30 months (ITT). Figure 2 shows the Kaplan-Meier plot of time to all-cause mortality by tafamidis dose.

Table 5: Summary of all-cause mortality events for ATTR-ACT (ITT; randomisation to 30 months)

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

Source: Table 2.5.3, p.80 and Table 2.5.12, p.107 of the July 2020 submission. Statistically significant results in bold.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; NE, not evaluable.
[a] Heart transplant or implantation of a cardiac mechanical assist device handled as death.
[b] Censored alive at time of analysis.

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



Subjects Remaning at Risk (Cumulative Events)

20MG	88	87	82	80	80	74	72	70	68	65	29	0
	0	1	6	8	8	14	16	18	20	23	24	24
80MG	176	172	170	164	155	148	144	139	132	128	70	0
	0	4	6	12	21	28	32	37	44	48	54	54
Placebo	177	173	171	163	161	150	141	131	118	113	51	0
	0	4	6	14	16	27	36	46	59	64	75	76

Source: Figure 15, p.128 of the ATTR-ACT Clinical Study Report.
Abbreviations: ITT, intention-to-treat.
Note: Heart transplant and implantation of a cardiac mechanical assist device handled as deaths.

6.16 All-cause mortality was lower in the tafamidis 80 mg (30.7%) and pooled tafamidis (29.5%) treatment arms at 30 months compared to placebo (42.9%), with the Cox-proportional hazard ratios demonstrating a statistically significant reduction in the risk of death of 31.0% for tafamidis 80 mg and 30.2% for pooled tafamidis, relative to placebo. There was no statistically significant difference in time to all-cause mortality between tafamidis 20 mg and placebo, although the ESC considered this was likely due to the smaller sample size in the tafamidis 20 mg treatment arm given the lower mortality point estimate for the 20 mg dose compared to the 80 mg dose. The observed treatment effect of tafamidis on all-cause mortality emerged after approximately 18 months of treatment, consistent with the slow, progressive disease trajectory of ATTR-CM.

6.17 Table 6 summarises the frequency of CV-related hospitalisations by tafamidis dose for the ATTR-ACT trial from randomisation to 30 months (ITT).

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

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

Source: Table 2.5.4, p.81 and Table 2.5.13, p.107 of the July 2020 submission. Statistically significant results in bold.
Abbreviations: CI, confidence interval; CV, cardiovascular; ITT, intention-to-treat; NYHA, New York Heart Association heart failure classification; SD, standard deviation; TTR, transthyretin.
[a] Cardiovascular-related hospitalisations per year calculated as (patient's number of cardiovascular hospitalisations)/(duration on study in years).
[b] Poisson regression analysis with treatment, TTR genotype, NYHA baseline classification (NYHA I & II; NYHA III), treatment-by-TTR genotype interaction, and treatment by NYHA baseline classification interaction terms as factors, adjusted for treatment duration.

6.18 Smaller proportions of patients experienced CV hospitalisation events in the tafamidis 20 mg (47.5%) and tafamidis 80 mg (54.5%) treatment arms compared to placebo (60.5%). The median number of hospitalisations per year was similar between the tafamidis 80 mg and placebo arms. However, when estimates were reported as mean number of hospitalisations per year, patients in the placebo arm had similar or slightly lower events (0.884) compared to tafamidis treated patients (0.976-1.010).

6.19 Comparisons between treatment arms based on a Poisson regression analysis with treatment, TTR genotype, NYHA baseline classification, treatment-by-TTR genotype interaction, and treatment-by-NYHA baseline classification interaction terms as factors, adjusted for treatment duration, showed the risk of CV hospitalisation was 33.9% lower for tafamidis 20 mg, 30.0% lower for tafamidis 80 mg and 32.4% lower for the pooled tafamidis arms compared to placebo. The reasons for the differences in estimates between mean and median CV hospitalisations per year and frequency of CV hospitalisation were unclear.

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

Table 7: Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV 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 CV hospitalisations at 30 months[b]	0.218	0.339	0.297	0.455
Finkelstein-Schoenfeld analysis versus placebo (p-value)	**p = 0.0048**	**p = 0.0030**	**p = 0.0006**	-

Source: Table 2.5.1, p.77 of the July 2020 submission. Statistically significant results in bold.
Abbreviations: CV, cardiovascular; ITT, intention-to-treat.
[a] Heart transplant or implantation of a cardiac mechanical assist device handled as death.
[b] Calculated as [patient's number of hospitalisations] / [study duration in years] among those alive at 30 months.

6.21 In the primary outcome for the ATTR-ACT trial, the Finkelstein-Schoenfeld prioritised pairwise comparison of all-cause mortality and CV 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%).

6.22 The results of the pairwise comparison were consistent with those for individual outcomes in that results for tafamidis 20 mg showed no statistically significant difference compared to placebo in all-cause mortality (although the ESC considered this was likely due to the smaller sample size in the tafamidis 20 mg treatment arm, as outlined in paragraph 6.16), but a statistically significant reduction in CV hospitalisations compared to placebo. Tafamidis 80 mg demonstrated statistically significant reductions in both all-cause mortality and CV hospitalisations compared to placebo.

6.23 For the 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. The PSCR highlighted that the submission had explored the impact of missing 6MWT data through pattern mixture analyses for the change from baseline to Month 30 in the distance walked during the 6MWT using two dropout pattern cases in the ITT population. The PSCR stated that the results of the pattern mixture analyses of the 6MWT were supportive of the key secondary analysis.

6.24 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.

Additional post hoc analyses

NYHA Class

6.25 At the July 2020 meeting the PBAC considered that the subgroup analyses of the ATTR-ACT trial indicate that the baseline risk of death varies substantially between subgroups. Therefore, even if constant relative treatment effects can be assumed between NYHA classes and TTR genotypes, the absolute benefit of tafamidis treatment will vary substantially between subgroups (para 6.28-31, tafamidis PSD, July 2020 PBAC meeting).

6.26 Tests for treatment effect interaction conducted for the July 2020 submission indicated that NYHA class is a treatment effect modifier for CV hospitalisation. The resubmission argued that the increased risk of hospitalisation was due to increased survival with tafamidis treatment in patients with severe heart failure. However, in the NYHA III subgroup, there was no statistically significant difference in all-cause mortality or CV mortality between patients treated with tafamidis versus placebo.

6.27 New post hoc analyses of ATTR-ACT data using a Finkelstein-Schoenfeld analysis of all-cause mortality and frequency of CV-related hospitalisation conducted for the resubmission, showed a pattern of decreased tafamidis treatment effect with increasing disease severity stratified by NYHA class and 6MWT quartiles (respectively) as measures of disease severity. The higher rates of CV-related hospitalisation associated with NYHA class III heart failure were not adequately explained, and were consistent with the pattern of decreasing treatment effect observed in the original post hoc analyses.

6.28 Table 8 shows the results of a new post hoc analysis of the ATTR-ACT and B3461045 long term extension data for all-cause mortality by NYHA baseline class at August 2019 and March 2020 data cut-offs, stratified by NYHA class I/II and III, conducted for the resubmission.

Table 8: All-cause mortality by NYHA baseline class I/II - ATTR-ACT/B3461045 long term extension data for Cohort A excluding patients randomised to tafamidis 20 mg (ITT; 1 Aug 2019 and 20 March 2020 cut-offs)

	ATTR-ACT + B3461045 (Cohort A)			
Events, n (%)	Baseline NYHA class I or II		Baseline NYHA class III	
	Tafamidis 80/61 mg	Pbo/ tafamidis[a]	Tafamidis 80/61 mg	Pbo/ tafamidis[a]
1 August 2019 cut-off (median follow up 51 months)				
N	121	114	55	63
All-cause mortality events[b]	41 (33.9%)	59 (51.8%)	34 (61.8%)	49 (77.8%)
Total deaths	35 (28.9%)	53 (46.5%)	32 (58.2%)	49 (77.8%)
Heart transplants	5 (4.1%)	6 (5.3%)	1 (1.8%)	0
Cardiac device implants	1 (0.8%)	0	1 (1.8%)	0
Censored[c]	80 (66.1%)	55 (48.2%)	21 (38.2%)	14 (22.2%)
Kaplan-Meier estimates of time to event (months) by Quartiles (95% CI)				
25%	39.0 (22.2, 47.6)	24.5 (20.7, 30.6)	12.7 (9.4, 18.8)	13.6 (8.1, 18.9)
50%	NE (NE, NE)	46.9 (36.7, NE)	28.1 (18.8, 41.7)	24.1 (19.1, 30.1)
75%	NE (NE, NE)	NE (NE, NE)	NE (38.8, NE)	38.4 (30.6, NE)
Cox proportional hazard ratio (95% CI)	**0.546 (0.366, 0.816)**		0.668 (0.426, 1.046)	
20 March 2020 cut-off				
N	121	114	55	63
All-cause mortality events[b]	45 (37.2%)	61 (53.5%)	34 (61.8%)	50 (79.4%)
Total deaths	39 (32.2%)	55 (48.2%)	32 (58.2%)	50 (79.4%)
Heart transplants	5 (4.1%)	6 (5.3%)	1 (1.8%)	0
Cardiac device implants	1 (0.8%)	0	1 (1.8%)	0
Censored[c]	76 (62.8%)	53 (46.5%)	21 (38.2%)	13 (20.6%)
Cox proportional hazard ratio (95% CI)	**0.556 (0.377, 0.822)**		0.647 (0.413, 1.013)	

Source: Tables 2.6.1 to 2.6.4, pp.70-73 of the resubmission. Statistically significant results in bold.
Abbreviations: CI, confidence interval; ITT, intention-to-treat; NE, not evaluable.
[a] Includes patients switching from the ATTR-ACT placebo arm, randomised to tafamidis meglumine 20 mg or 80 mg (1:2 ratio) on enrolment into B3461045, and then all migrated to tafamidis 61 mg (free acid formulation) after the July 2018 protocol amendment.
[b] Heart transplant or implantation of a cardiac mechanical assist device handled as death.
[c] Censored alive at time of analysis.

6.29 In the analysis above, in patients with baseline NYHA class I/II, all-cause mortality was lower in the tafamidis 80/61 mg treatment arm at the August 2019 (33.9%) and March 2020 (37.2%) cut-offs compared to placebo/tafamidis (51.8% and 53.5% respectively), with the Cox-proportional hazard ratios demonstrating a statistically significant reduction in the risk of death of 45.4% and 44.4% respectively, relative to placebo/tafamidis. There was no statistically significant difference in all-cause mortality between tafamidis 80/61 mg and placebo/tafamidis in patients with baseline NYHA class III heart failure at either cut-off dates.

6.30 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. For example, it was unclear whether patients in the placebo/tafamidis treatment arms received ≥18 months of treatment, which was the duration of tafamidis treatment that patients had received before differences in

all-cause mortality were observed in the ATTR-ACT trial. Given the differences in tafamidis dose intensity, duration of treatment and drug exposure, the results of the post hoc subgroup analyses should be interpreted with caution.

Dosing: 80 mg (bioequivalent to 61 mg free acid) versus 20 mg

6.31 At the July 2020 meeting, the PBAC noted that results for key outcomes were similar for the 20 mg and 80 mg tafamidis dose strengths, and that adequate justification for the 80 mg dose rather than the 20 mg had not been provided (para 7.10, tafamidis PSD, July 2020 PBAC meeting).

6.32 The resubmission presented a new post hoc subgroup analysis by baseline tafamidis dose allocation, for the combined ATTR-ACT and B3461045 data sets, at data points prior to (1 August 2018 data cut-off) and after (1 August 2019 data cut-off) the July 2018 protocol amendment which migrated all patients to the tafamidis 61 mg (free acid) dose regimen. The resubmission acknowledged that the B3461028 study was not powered to differentiate tafamidis dose strengths by treatment effect.

6.33 The post hoc subgroup analysis showed reduced all-cause mortality in patients randomised to tafamidis 80 mg at baseline compared to patients allocated to tafamidis 20 mg across all analyses at the 1 August 2019 data point, with a statistically significant reduction in the risk of all-cause mortality in the unadjusted analysis of 30.0% (hazard ratio 0.700; 95% CI: 0.501, 0.979). These data, published by Damy et al. 2020, were also presented in the PSCR. However, there were no statistically significant differences between baseline tafamidis dose strengths at the 1 August 2018 data point. Further, no data was provided from the March 2020 analysis for patients allocated to 20 mg and 80 mg doses. The ESC noted that the difference was only statistically significant in the 1 August 2019 analysis, which was conducted after patients in the 20 mg arm had transitioned to the higher dose (and thus the 20 mg arm included outcomes for patients who had received the higher dose for up to a year).

6.34 The combined ATTR-ACT and B3461045 study treatment arms included patients continuing tafamidis doses from the ATTR-ACT trial or switching to tafamidis 80 mg or 20 mg dose strengths from the ATTR-ACT trial placebo arm (randomised on a 2:1 ratio respectively), with all patients in both treatment arms migrating to the tafamidis 61 mg formulation after the July 2018 protocol amendment. Given the differences in tafamidis dose intensity, duration of treatment and drug exposure, particularly in patients switching from placebo in the ATTR-ACT trial to tafamidis in the B3461045 extension study, the results of the subgroup analysis by baseline tafamidis dose allocation were unreliable, and should be interpreted with caution.

Comparative harms

6.35 The comparative harms presented in the resubmission were unchanged from the July 2020 submission.

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

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

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

Source: Tables 2.5.1 and 2.5.2, pp.64-65 of the resubmission; Tables 2.5.8 and 2.5.9, pp. 58-59 of the July 2020 commentary.
Abbreviations: AEs, adverse events; SAEs serious adverse events.
[a] Median duration of follow-up in the ATTR-ACT trial was not reported in the submission or Clinical Study Report.

6.37 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.

6.38 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%).

6.39 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 2019 to 15 May 2020, and no new safety risks were 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.

Benefits/harms

6.40 Benefits and harms based on the results of the direct ATTR-ACT trial were unchanged from the July 2020 submission. Insufficient information was available to assess benefits and harms in the subgroup of patients with NYHA class I/II at baseline.

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

- Approximately 12 fewer patients will experience an all-cause mortality event.
- Approximately 10 fewer patients will experience a CV mortality event.
- Approximately 6 fewer patients will experience CV-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

6.42 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 alone.

6.43 The PBAC considered that the claim was reasonable in terms of efficacy, however, a moderate level of uncertainty remained with respect to the magnitude of the benefit.

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

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

Economic analysis

6.45 The resubmission presented a modelled economic evaluation of tafamidis compared to best supportive care for the treatment of patients with ATTR-CM. The economic evaluation was based on the ATTR-ACT trial with additional modelled data. The economic evaluation was presented as a cost-effectiveness/cost-utility analysis.

Table 10: Summary of model structure, key inputs and rationale for the current model and July 2020 model

Component	July 2020 model	Current model
Treatments	Tafamidis versus best supportive care	Tafamidis versus best supportive care
Time horizon	20 years in the model base case versus 2.5 years in the ATTR-ACT trial 51% of incremental costs and 93.9% of incremental QALYs were generated in the extrapolated period.	20 years in the model base case versus 2.5 years in the ATTR-ACT trial. 59.6% of incremental costs and 91.5% of incremental QALYs were generated in the extrapolated period.
Outcomes	Life years; quality adjusted life years	Life years; quality adjusted life years
Methods used to generate results	Markov state transition model	Markov state transition model
Health states	- Alive - Dead	- Alive, NYHA I/II, CV hospitalisation ≤6 months - Alive, NYHA I/II, no CV hospitalisation ≤6 months - Alive, NYHA III/IV, CV hospitalisation ≤6 months - Alive, NYHA III/IV, no CV hospitalisation ≤6 months - Dead
Cycle length	6 months	6 months
Patient characteristics	Distribution of patients across NYHA classes (NYHA I/II, NYHA III) based on baseline values from the ATTR-ACT trial.	All patients begin the model with NYHA I/II without a recent CV hospitalisation.

Component	July 2020 model	Current model
Transition probabilities	Transition probabilities for survival in the best supportive care arm were estimated by fitting a Gompertz curve to ATTR-ACT trial data. Transition probabilities for survival in the tafamidis arm were estimated by fitting a gamma curve to ATTR-ACT trial and extension study data. The probability of having a CV hospitalisation was estimated from post hoc analyses of ATTR-ACT data by treatment arm and duration of exposure within each NYHA class. The probability of CV hospitalisation was assumed to remain constant over time. The probability of discontinuation in the tafamidis arm was estimated by fitting a log normal curve to ATTR-ACT data.	Individual patient data from the ATTR-ACT trial (subgroup with baseline NYHA class I/II) were used to derive transition probabilities of 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 assumed to be constant, based on weighted averages of the first five 6-month cycles. The number of hospitalisations per hospitalised patient was derived for each treatment arm based on data from the ATTR-ACT trial. 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 model did not explicitly incorporate a stopping rule consistent with the requested restriction, whereby patients with NYHA class IV discontinue tafamidis treatment.
Utilities	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 NYHA class (NYHA I/II or III). Weighting between NYHA classes for NYHA class I/II based on distribution at baseline (12.3%/87.7%). NYHA class I/II: 0.792 for tafamidis; 0.759 for best supportive care NYHA class III: 0.606 for tafamidis; 0.609 for best supportive care No additional disutility assumed for CV hospitalisation.	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 NYHA class (NYHA I/II or III/IV). Weighting between NYHA classes for NYHA class I/II based on 50%/50% distribution; and for NYHA class III/IV based on 66.7%/33.3% distribution. NYHA class I/II: 0.815 for tafamidis; 0.806 for best supportive care NYHA class III/IV: 0.534 for tafamidis; 0.461 for best supportive care Given that patients would be required to discontinue tafamidis when they progress to class IV, the ESC considered that the difference in utilities between the tafamidis and best supportive care arms in the class III/IV health state was likely overestimated. No additional disutility assumed for CV 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 ($7,927 per treated subject). Tafamidis drug costs were estimated based on the proposed effective DPMQ ($[redacted] per 6-month cycle). Cardiovascular hospitalisation costs estimated as the weighted average of 98 CV-related AR-DRG items. Cost estimates inflated using AIHW health	A similar approach was used to cost ATTR-CM diagnosis, but the costs of scintigraphy were based on localised bone study MBS items only (following advice from MSAC that whole body scintigraphy items would overestimate costs; MSAC PSD 1584, 76th MSAC meeting 1-2 August 2019) ($14,621 per treated subject (corrected during the evaluation); the increase is mainly due to an increase in the number of screened individuals required to identify one treated case [from 5.86 to 10.84]). Tafamidis drug costs were estimated based on the proposed effective DPMQ ($[redacted] per 6-month cycle;

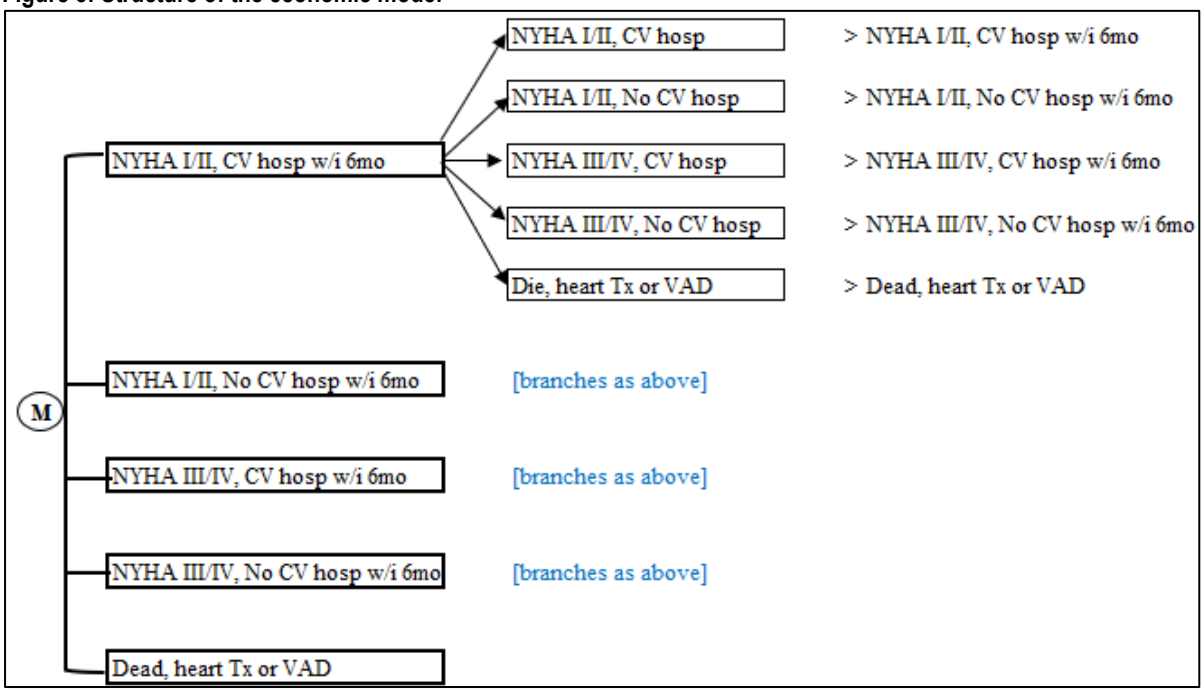
Component	July 2020 model	Current model
	inflation index ($7,940 per event). Disease management costs were estimated from published studies (Ademi 2014, Ford 2012). Cost estimates inflated using AIHW health inflation index (NYHA I/II $97; NYHA III $128 per 6-month cycle). Terminal care costs were estimated based on the assumption that half of all deaths would be preceded by a CV-related hospitalisation ($3,970 per event).	the difference was due to the reduction in requested effective DPMQ from $[redacted] to $[redacted]). CV hospitalisation costs estimated as the weighted average of 93 CV-related AR-DRG items. Cost estimates inflated using AIHW health inflation index ($7,244 per event). Disease management costs were estimated from published studies (Ademi 2014, Ford 2012). Cost estimates inflated using AIHW health inflation index (NYHA I/II $1,033; NYHA III/IV $1,466 per 6-month cycle; correcting for monthly estimates assumed to be annual estimates). Terminal care costs were estimated based on the assumption that half of all deaths would be preceded by a CV-related hospitalisation ($3,622 per event).

Source: Table 3.1.3, p130 and Sections 3.3-3.6, pp139-156 of the resubmission; Section 3, pp180-208 of the July 2020 submission
Abbreviations: AIHW, Australian Institute of Health and Welfare; AR-DRG, Australian Refined Diagnosis Related Groups; CV, cardiovascular; DPMQ, dispensed price for maximum quantity; EQ-5D-3L, EuroQoL 5 dimension 3 level instrument; MBS, Medicare Benefits Schedule; NYHA, New York Heart Association

6.46 The resubmission stated that a new model structure was adopted to address the concerns raised by the PBAC in its previous consideration (patients remain in baseline NYHA class; constant probability of CV hospitalisation; all CV hospitalisations non-fatal; treatment effect maintained following treatment discontinuation).

6.47 The new model structure is illustrated in the figure below.

Figure 3: Structure of the economic model



Source: Figure 3.1.2, p131 of the resubmission
Abbreviations: CV hosp, cardiovascular hospitalisation; mo, months; NYHA, New York Heart Association; Tx, transplant; VAD, ventricular assist device; w/i, within

6.48 Patients begin the model in the 'NYHA I/II no CV hospitalisation within 6 months' health state. During each 6-month cycle, patients can transition to another NYHA class and/or experience hospitalisation, or die. Additionally, patients in the tafamidis arm may discontinue drug treatment in each cycle.

6.49 While the July 2020 model assumed patients remain in their baseline NYHA class over the duration of the model, the new model structure allowed patients to progress and regress between NYHA class categories (NYHA I/II and NYHA III/IV).

6.50 The new model structure, with transitions between NYHA class, CV hospitalisation and death informed by individual patient data from the ATTR-ACT trial, linked CV hospitalisation and mortality, which was not explicitly modelled in the previous submission.

6.51 In the resubmission, individual patient data from the subgroup of patients from the ATTR-ACT trial with NYHA class I/II at baseline were used to derive transition probabilities for movement between NYHA class I/II and III/IV, CV-related hospitalisations, and death, over five six-monthly intervals (corresponding to the first five model cycles). Separate transition probabilities were estimated for patients in the tafamidis and best supportive care arms. The individual transitions between health states could not be verified during the evaluation.

6.52 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, which was acknowledged in the resubmission. For example, there were a number of inconsistencies in transition probabilities due to the small number of patients informing transitions (e.g. higher probabilities of death for patients with NYHA class I/II versus NYHA class III/IV; and for patients without a recent hospitalisation versus patients with a recent hospitalisation).

6.53 Transition probabilities beyond 30 months were assumed to be constant, based on weighted average estimates of the first five cycles of transitions from the ATTR-ACT trial. The use of average transition probabilities for cycles 6+ resulted in constant transition probabilities over time for death and NYHA class transitions which was not appropriate, as disease progression and mortality would generally be expected to increase with age and duration of disease. This approach resulted in probabilities of death from several health states that were lower than Australian general population estimates (see Table 12), which was not clinically plausible given the poor prognosis of ATTR-CM. The PSCR presented the results of a sensitivity analysis in which the risk of death was increased by 5% (in relative terms) per six-month cycle, from cycle 7 (Year 4) onwards. This resulted in an ICER of $155,000 to <$255,000 per QALY (using the corrected model) versus the base case ICER of $155,000 to <$255,000 per QALY, and all patients in the tafamidis arm had died by 20 years; all patients in the best supportive care arm had died by 15 years. The ESC considered that this analysis did not adequately address the issue, which would require more comprehensive changes to the model. The pre-PBAC response conducted a similar analysis but using a 5.3% (rather than 5%) increase in the risk of death per six-month cycle, which it stated was based on mortality data from the AIHW General Record of Incidence of Mortality books for 2018[1]. This analysis increased the ICER to $155,000 to <$255,000 per QALY (using the corrected model).

6.54 The table below shows health state transitions for heart failure, simplified by merging states with and without recent cardiovascular hospitalisation.

[1] Australian Institute of Health and Welfare (AIHW) 2020. General Record of Incidence of Mortality (GRIM) books 2018: All causes combined. Canberra: AIHW.

Table 11: Simplified health state transitions (merging cardiovascular hospitalisation categories); weighted average across the five six-month periods of the ATTR-ACT trial

	To			
From	**Death**	**NYHA I/II**	**NYHA III/IV**	**Total**
Tafamidis				
NYHA I/II	1.7%	84.7%	13.6%	100.0%
NYHA III/IV	10.0%	36.4%	53.6%	100.0%
Best supportive care				
NYHA I/II	4.5%	75.4%	20.1%	100.0%
NYHA III/IV	10.2%	29.5%	60.2%	100.0%

Source: constructed during the evaluation based on Tables 3.4.1 and 3.4.2, pp146-147 of the resubmission
Abbreviations: NYHA, New York Heart Association

6.55 The ESC noted that the model estimated that 36.4% and 29.5% of patients would experience an improvement from NYHA class III/IV to class I/II over six months in the tafamidis and best supportive care arms, respectively. The PBAC considered that a proportion of patients may improve in the first cycle, but that this was unlikely to continue for the duration of the model.

6.56 As in the previous model, the current model inappropriately assumed maintenance of treatment effect following treatment discontinuation, with the same treatment effects applied in Year 18 (with only 32% of patients on treatment) as the first 2.5 years (with 86% of patients on treatment). The PBAC previously considered that this was inappropriate as increasing proportions of patients discontinue over time and spend longer durations without therapy. This represented a major bias in favour tafamidis as it resulted in substantially reduced drug costs without reduced efficacy. The PSCR argued that the model used intention-to-treat results from ATTR-ACT and hence the treatment effects observed took into account treatment discontinuation. However, the ESC considered that while this may be reasonable for the 30 month trial period, the implicit association between clinical outcomes and discontinuations observed in the trial was unlikely to be maintained over time. The pre-PBAC response attempted to account for treatment discontinuation by conducting a sensitivity analysis in which, from Cycle 7 onwards, the probabilities of death from the placebo arm were applied to the proportions of patients who discontinue tafamidis, which increased the ICER to $155,000 to <$255,000/QALY gained (using the corrected model). No adjustment was made to any other transition probabilities, for example, tafamidis-treated patients who discontinued treatment maintained a treatment benefit in terms of hospitalisation and NYHA progression/regression. This generated an indirect mortality benefit, and thus the sensitivity analysis only partially corrected the issue.

6.57 The ESC considered potential alternative model structures and modelling approaches. The ESC considered that:

- Given the sparsity of data arising from the use of composite NYHA class/hospitalisation health states, it may be appropriate to apply state-specific CV hospitalisation rates to inform the estimation of the health state costs (including

exploration of CV hospitalisation rates increasing over time), rather than specifying separate CV hospitalisation states. Given the resubmission appropriately altered the model so that patients no longer remain in the same NYHA class over the duration of the model, this may also address the PBAC's previous concerns that a constant probability of hospitalisation was applied over the duration of the model (paragraph 7.12, tafamidis PSD July 2020).

- It may be appropriate to use parametric functions to estimate times to events, e.g. time to NYHA class III/IV (with and without tafamidis), and time to death (by NYHA state and tafamidis exposure).
- Additional justification is required to support the modelled regression from NYHA class III/IV to class I/II.
- As per the previous submission, a method to link discontinuations to treatment effectiveness would be required.
- Parameterisation of any model structure would not be straightforward.

6.58 Key drivers of the economic model are summarised in the table below.

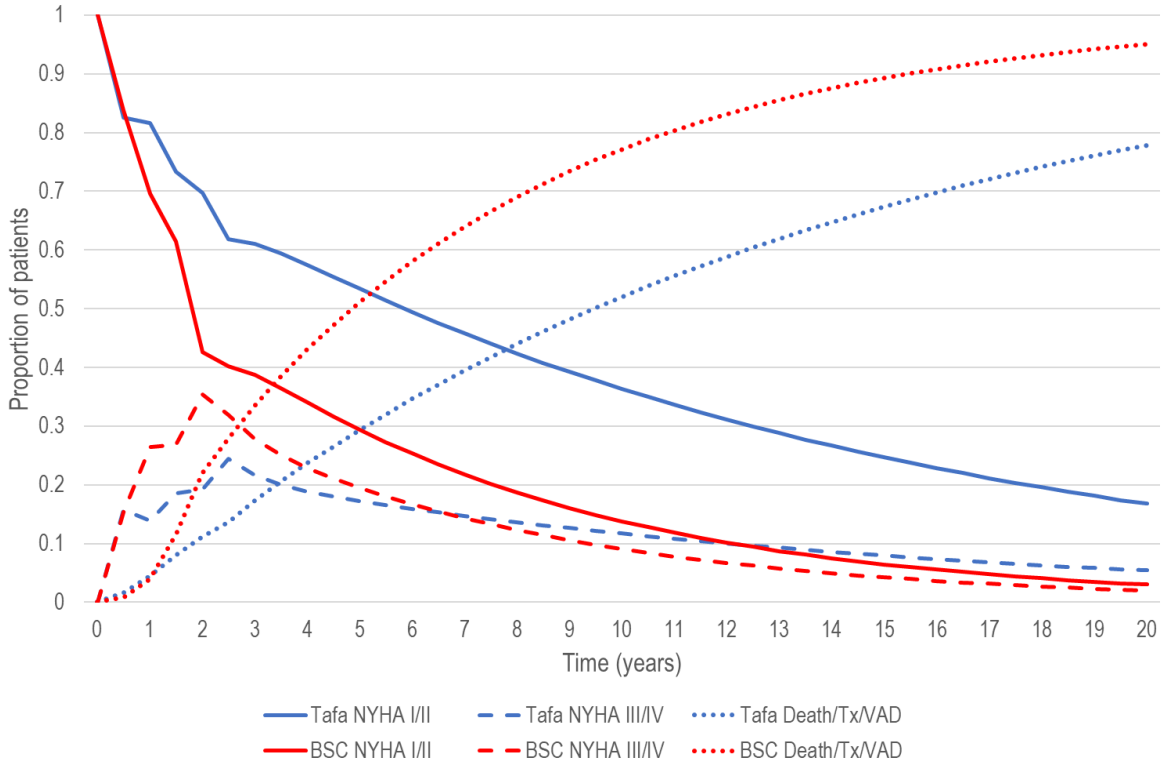
Table 12: Key drivers of the model

Description	Method/Value	Impact
Mortality	In the model, 6-monthly probabilities of all-cause mortality beyond 2.5 years were based on weighted average estimates of mortality derived from individual patient data over the 30-month duration of the ATTR-ACT trial. As a result, constant probabilities of death were applied in the model from 2.5 years. The model generated probabilities of death that were lower than Australian general population estimates for several health states (both NYHA class I/II and III/IV, with and without recent hospitalisation) and for both treatment arms, which was not clinically plausible given the poor prognosis of ATTR-CM. After 20 years, 5% of patients in the best supportive care arm and 22% of patients in the tafamidis arm were still alive at age 94 years. The estimates of survival for the tafamidis arm exceeded survival in the Australian population, which was not clinically plausible.	Unclear
Treatment persistence	As in the previous model, treatment discontinuation rates were applied to drug costs only, with no impact on survival, NYHA class, or CV hospitalisations. In the model, the same treatment effects were applied in Year 18 (with only 32% of patients on treatment and accruing drug costs) as the first 2.5 years (with 86% of patients on treatment). The PBAC previously considered that it was inappropriate to apply treatment discontinuation rates to drug costs only, as the implicit association between clinical outcomes and discontinuations observed in the trial period is unlikely to be maintained over time (paragraph 6.47, tafamidis PSD, July 2020 PBAC meeting). The evaluation considered that an alternative approach would be to assume no benefit or cost when tafamidis is discontinued.	High, favours tafamidis
Time horizon	The resubmission nominated a 20 year time horizon for the economic analysis on the basis that this was appropriate to capture the majority of costs and benefits in an older population with ATTR-CM. The same time horizon was used in the July 2020 submission. A 20-year time horizon may not be appropriate given that the target population represents an older age group (mean baseline age in the ATTR-ACT trial was approximately 74 years) who are likely to have multiple co-morbidities (paragraph 6.54, tafamidis PSD, July 2020 PBAC meeting). The resubmission stated that a 20 year time horizon was effectively a lifetime time horizon for the target population aged 74 years at baseline.	High, favours tafamidis

Source: Constructed during the evaluation.
Abbreviations: CV, cardiovascular; NYHA, New York Heart Association; TTR-CM, cardiac transthyretin amyloidosis;

6.59 The model trace in the figure below shows the proportion of patients remaining in each health state (NYHA class I/II; NYHA class III/IV; dead) over the 20-year model time horizon. For each NYHA class category (I/II and III/IV), the proportions of patients with and without CV hospitalisations in the 6-month cycle have been combined.

Figure 4: Model trace



Source: Constructed during the evaluation based on Economic Model - tafamidis - Nov2020 Excel workbook
Abbreviations: BSC, best supportive care; NYHA, New York Heart Association; Tafa, tafamidis; Tx, heart transplant; VAD, ventricular assist device.

6.60 The model trace shows limited convergence of the curves between treatment arms over the 20 year time horizon. The resubmission stated that a 20-year time horizon was effectively a lifetime time horizon for the target population aged 74 years at baseline. However, the model estimated that after 20 years, 5% of patients in the best supportive care arm and 22% of patients in the tafamidis arm are still alive.

6.61 The results of the modelled economic evaluation are summarised below.

Table 13: Results of the economic evaluation

Component	Tafamidis	Best supportive care	Increment
Costs	$ [redacted]	$31,949	$ [redacted]
Life years	7.7464	5.2999	2.4465
Incremental cost per life year gained			**$** [redacted] [1]
Costs	$ [redacted]	$31,949	$ [redacted]
QALYs	5.8249	3.6392	2.1856
Incremental cost/QALY gained			**$** [redacted] [2]

Constructed during the evaluation based on Economic Model - tafamidis - Nov2020 Excel workbook
Note: Costs were corrected during evaluation for errors in the calculation of acute disease costs and disease management costs, and the inappropriate use of MBS benefit rather than MBS fee.
The redacted values correspond to the following ranges:
[1]*$135,000 to <$155,000/LY gained*
[2]*$155,000 to <$255,000/QALY gained*

6.62 Based on the economic model presented in the resubmission, treatment with tafamidis was associated with an incremental cost per QALY gained of $155,000 to <$255,000 compared to best supportive care for the treatment of patients with ATTR-CM. The incremental cost per QALY gained was $255,000 to <$355,000 in the previous submission. The ESC considered the incremental cost-effectiveness ratio (ICER), while lower than the previous submission, remained high and was not reliable due to the issues discussed above.

6.63 Applying the resubmission's proposed effective DPMQ in the previous and current models results in ICERs of $115,000 to <$135,000 per QALY gained and $155,000 to <$255,000 per QALY gained, respectively. Thus, overall the resubmission's model was more conservative than the model in the previous submission.

6.64 The results of sensitivity analyses presented in the resubmission and conducted during the evaluation are summarised below.

Table 14: Results of key sensitivity analyses

Analyses	Incremental cost	Incremental QALYs	ICER
Base case	**$** [redacted]	**2.1856**	**$** [redacted][1]
Time horizon (base case: 20 years)			
10 years	$ [redacted]	1.3198	$ [redacted][1]
15 years	$ [redacted]	1.8520	$ [redacted][1]
Patient population (base case: 100% NYHA class I/II at baseline)			
68% NYHA class I/II; 32% NYHA class III/IV at baseline	$ [redacted]	1.3953	$ [redacted][1]
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 five trial-based six-monthly cycles)			
Cycles 1-5, 6+: weighted average of cycles 1-5; missing data deleted	$ [redacted]	2.1422	$ [redacted][1]
Cycles 1-5, 6+: weighted average of cycles 1-5; LOCF to impute missing data	$ [redacted]	1.8577	$ [redacted][1]
Cycles 6+: based on data from extension study [b]	$ [redacted]	1.4295	$ [redacted][1]
Treatment persistence extrapolations (base case: discontinuations in the tafamidis treatment arm extrapolated using an exponential function)			
Discontinuations extrapolated using lognormal function	$ [redacted]	2.1856	$ [redacted][1]
No discontinuations after month 30 (discontinuation curve same as survival curve from month 30)[a]	$ [redacted]	2.1856	$ [redacted][1]
No discontinuations over the course of the model (discontinuation curve same as survival curve)[a]	$ [redacted]	2.1856	$ [redacted][1]
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)			
Treatment independent NYHA utility values (based on Ademi 2014 publication)	$ [redacted]	1.8918	$ [redacted][1]
Treatment independent NYHA utility values (based on best supportive care arm)[a]	$ [redacted]	2.0059	$ [redacted][1]
Treatment independent NYHA utility values (based on tafamidis arm)[a]	$ [redacted]	2.0217	$ [redacted][1]

Source: Table 3.9.1, p162 and Economic Model - tafamidis - Nov2020 Excel workbook provided with the resubmission
Abbreviations: EQ-5D-3L, EuroQoL- 5 dimension 3 level questionnaire; IPD, individual patient data; LOCF, last observation carried forward; NYHA, New York Heart Association
Note: Costs were corrected for errors in the calculation of acute disease costs and disease management costs, and the inappropriate use of MBS benefit rather than MBS fee.
[a] Analyses conducted during the evaluation.
[b] This was an analysis conducted by the sponsor using data in the 'IPD12Ext' worksheet of the 'Economic Model - tafamidis - Nov2020' model spreadsheet. Limited details of this analysis were provided in the submission and the individual patient data could not be verified during evaluation. The Cycle 6+ estimates were based on a weighted average of the first 5 cycles; and were available for the tafamidis arm only. Additional assumptions were required to generate estimates for the supportive care arm (same relative differences between tafamidis and best supportive care as in weighted average transition probabilities based on the ATTR-ACT trial; same probabilities of cardiovascular hospitalisation).
The redacted values correspond to the following range:
[1]$155,000 to <$255,000/QALY gained

6.65 The sensitivity analyses indicated that the model was most sensitive to the time horizon, extrapolation of transition probabilities beyond the trial data and treatment persistence.

6.66 However, the sensitivity analyses did not adequately capture the uncertainty associated with the model, as it was not possible to adequately explore the impact of many components of the economic model (e.g. assumptions regarding constant probabilities of mortality and CV hospitalisation, maintenance of treatment effect

following treatment discontinuation). For example, the ESC noted that the sensitivity analyses regarding treatment persistence did not assess the impact of removing the tafamidis treatment effect (e.g. by assuming the same transitions as best supportive care) following discontinuation. The ESC recommended a revised model structure and parameterisation.

6.67 The PBAC noted that combining the two sensitivity analyses presented in the pre-PBAC response (relating to the constant risk of death and maintenance of treatment effect following treatment discontinuation, see paragraphs 6.53 and 6.56) resulted in an incremental cost per QALY gained of $155,000 to <$255,000 (using the corrected model). Due to the incomplete adjustment to transition probabilities for treatment discontinuation, this was a likely underestimate of the ICER.

Drug cost/patient/year

6.68 The tafamidis drug cost per patient per year was $[redacted], based on 12.175 scripts per patient per year. The approach to estimating drug cost was consistent across the economic analysis and financial estimates, however different approaches were used to calculate the proportion of patients on treatment. The estimates informing the economic model were based on the subgroup of patients with NYHA class I/II at baseline, whereas estimates informing the financial estimates were based on patients with NYHA class I/II/III at baseline. The different approaches generated similar estimates of patients remaining on treatment over a six-year period.

Table 15: 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)	-	$[redacted]	$[redacted]
Number of scripts per year	-	12.175(=365.25/30)	12.175(=365.25/30)
Cost per year	-	$[redacted]	$[redacted]
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: 89.7% Year 3: 78.4% Year 4: 68.5% Year 5: 59.4% Year 6: 51.6%	Year 1: 100%[b] Year 2: 86.0% Year 3: 74.0% Year 4: 63.6% Year 5: 54.7% Year 6: 47.0%

Source: Constructed during the evaluation using Economic Model - tafamidis - Nov2020 and Utilisation and cost model – tafamidis spreadsheets provided with the resubmission

[a] Proportions of patients alive and on treatment at the start of each year from the economic model. Drug discontinuation estimated by fitting an exponential curve to ATTR-ACT data for the subset of patients with NYHA class I/II at baseline; mortality estimated based on individual patient data from the ATTR-ACT trial subgroup with baseline NYHA class I/II over the first five 6-month periods, with estimates beyond 30 months based on the weighted average of the first five 6-month periods.

[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 3% was based on discontinuations in the tafamidis 80 mg arm in those still alive at the end of the ATTR-ACT trial, adjusted to derive an annual estimate (8%×12/30). Estimates were based on the population with NYHA class I/II/III at baseline.

Estimated PBS usage & financial implications

6.69 This resubmission was not considered by DUSC.

6.70 The resubmission used an epidemiological approach to estimate the utilisation and financial impact of listing tafamidis on the PBS. The approach was substantially revised compared to the July 2020 submission, with new data sources used to estimate prevalence of ATTR-CM, revised diagnosis and uptake rates, new sources used to inform the distribution of patients across NYHA classes, and a revised effective price of tafamidis.

6.71 Key inputs are summarised in the table below.

Table 16: Key inputs for financial estimates

Data	Value	Source	Comment
Proportion of population with heart failure	Males: 65-74 yrs - 3.34% 75-84 yrs - 6.92% 85-100 yrs 12.58% Females: 65-74 yrs – 2.68% 75-84 yrs – 5.71% 85-100 yrs 11.01%	Liew et al., 2020 a retrospective cohort study of primary care data to estimate the prevalence and annual incidence of HF in the general Australian community.	This survey was based on data from bulk-billing GP practices, which tend to have higher rates of itinerant attendances and therefore may not have chronic conditions recorded. These estimates may underestimate rates of heart failure.
Amyloid deposition rates	Males: 65-74 yrs – 1.44% 75-84 yrs – 2.46% 85-100 yrs 6.15% Females: 65-74 yrs – 0.17% 75-84 yrs – 0.4% 85-100 yrs – 1.69%	Prevalence of cardiac amyloidosis was drawn from Cuscaden et al. 2020, an Australian study of images taken from the medical records of patients undergoing bone scans for non-cardiac reasons.	These proportions were based on incidental findings in patients undergoing scintigraphy for non-cardiac indications, including oncology and musculoskeletal. Additionally, the values in this study are based on very small patient numbers (n=15 with positive bone scans, including only one female). The prevalence rate is likely to be higher in patients with heart failure.
Prevalence of variant ATTR-CM	0.00052%	A systematic review of systemic amyloidosis diagnosis, prognosis, and therapies by Gertz and Dispenzieri, 2020.	The authors acknowledged that the published estimates were likely to underestimate the true prevalence, due to poor recognition and diagnosis rates for amyloidosis.
Percentage of patients diagnosed with ATTR-CM	Year 1 - 30% Year 2 - 40% Year 3 - 50% Year 4 - 60% Year 5 - 70% Year 6 - 80%	Assumption based on expert opinion that ATTR-CM is grossly underdiagnosed.	The extent to which ATTR-CM is underdiagnosed is uncertain. The published estimates used to determine the prevalence of ATTR-CM may already account for the under-diagnosis of these patients, and therefore application of this factor may further reduce the population unnecessarily.
Percentage of diagnosed patients with NYHA classes I-III	Year 1 - 85% Year 2 - 90% Year 3 - 95% Year 4 - 95% Year 5 - 95% Year 6 - 95%	Estimate.	The source for this estimate was unclear. It may be based on the estimate of the proportion of patients with Gilmore stage III, which does not align with NYHA class IV. No evidence was presented to support the assumption of declining proportions of patients with NYHA class IV.

Data	Value	Source	Comment
Percentage of patients diagnosed with NYHA class III as a proportion of NYHA classes I-III	Year 1 - 35% Year 2 - 30% Year 3 - 25% Year 4 - 25% Year 5 - 20% Year 6 - 20%	Estimate.	The source of this estimate was unclear. No evidence was presented to support the declining proportions of patients with NYHA class III over time.
Percentage of NYHA class III patients with non-persistent class III disease	21%	Based on placebo treated patients with NYHA class III at baseline who transitioned to NYHA class I-II at 6 months in the ATTR-ACT trial (13/63; 21%)	Given the subjective nature of NYHA classification and the proposed restriction limiting treatment to NYHA class I and II, it is likely that the proportion of patients classified as non-persistent NYHA class III will be higher than estimated in the resubmission. The PSCR noted that clinical experts consulted indicated that this may be as high as 50%.
Proportion of patients treated with tafamidis	Year 1 - 50% Year 2 - 55% Year 3 - 60% Year 4 - 65% Year 5 - 70% Year 6 - 75%	Assumption	No justification for this assumption was provided. As the first agent listed for ATTR-CM, uptake rates for tafamidis may be higher than estimated in the resubmission.

Source: Compiled during the evaluation based on Utilisation and cost model - tafamidis spreadsheet provided with the resubmission.
Abbreviations: ABS, Australian Bureau of Statistics; ATTR-CM, cardiac transthyretin amyloidosis; DPMQ, dispensed price for maximum quantity; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

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

Table 17: Estimated use and financial impact of tafamidis on the PBS/RPBS

	2021	2022	2023	2024	2025	2026
Estimated utilisation of tafamidis						
Prevalent population with ATTR-CM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage diagnosed with ATTR-CM	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Number diagnosed with ATTR-CM	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage diagnosed patients with NYHA classes I-III	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients diagnosed with NYHA classes I-III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of NYHA class I-III patients with class III	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Patients with NYHA class III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients diagnosed with non-persistent NYHA class III ([redacted]%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with NYHA class I-II and non-persistent class III	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Percentage of patients initiating treatment with tafamidis	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%

	2021	2022	2023	2024	2025	2026
Number of patients initiating treatment with tafamidis[a]	[redacted][b,7] ([redacted])[7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Number of continuing patients from previous year (less [redacted]% who die; less [redacted]% who discontinue)	-	[redacted][a, 7] ([redacted])[7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Grandfathered patients from product familiarisation program[c]	[redacted][7]	[redacted][7]	0	0	0	0
Grandfathered patients continuing from previous year	-	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]	[redacted][7]
Total number of patients treated per year	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Scripts for initial patients (< 500 scripts per year; patients initiating in 2021 receive < 500 scripts only)	[redacted][7]	[redacted][9]	[redacted][9]	[redacted][8]	[redacted][9]	[redacted][9]
Scripts for continuing patients (< 500 scripts per year)	-	[redacted][8]	[redacted][9]	[redacted][10]	[redacted][10]	[redacted][10]
Scripts for discontinuing patients (< 500 scripts per year; patients who discontinued in 2021 receive < 500 scripts only)	[redacted][7]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]
Total number of scripts per year	[redacted][7]	[redacted][10]	[redacted][10]	[redacted][11]	[redacted][11]	[redacted][11]
Cost of tafamidis to the PBS/RPBS (effective price)						
Net of tafamidis to PBS/RPBS	$[redacted][1]	$[redacted][2]	$[redacted][4]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to MBS	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net cost to PBS/RPBS/MBS	$[redacted][1]	$[redacted][2]	$[redacted][4]	$[redacted][6]	$[redacted][6]	$[redacted][6]
July 2020 submission						
Total no. scripts per year	[redacted][8]	[redacted][9]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Net cost to PBS/RPBS	$[redacted][3]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to MBS	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]	$[redacted][1]
Net cost to PBS/RPBS/MBS	$[redacted][3]	$[redacted][5]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Tables 4.2.4, p.175; 4.2.5, p.176; 4.2.6, p.177; 4.2.8, p.178 of the resubmission; Utilisation and cost model - tafamidis spreadsheet.
Abbreviations: ATTR-CM, cardiac transthyretin amyloidosis; NYHA, New York Heart Association classification.

[a] Uptake is calculated based on the number of patients with NYHA class I-II or non-persistent class III minus the number of patients continuing tafamidis treatment from the previous year.

[b] The resubmission inappropriately adjusted the number of initiating and continuing patients in year 1 to be 2 out of 12 months (1/6th of calculated initiating and continuing patients), as listing was not anticipated to occur until November 2021. The number for the full year is presented in parentheses.

[c] Grandfathered patients were greater in Year 2 than Year 1, as the submission anticipated listing in November 2021. Most grandfathered patients therefore were anticipated to initiate in Year 2.

The redacted values correspond to the following ranges:

[1]$0 to <$10 million

[2]$50 million to <$60 million

[3]$20 million to <$30 million

[4]$90 million to <$100 million

[5]$80 million to <$90 million

[6]*$100 million to <$200 million*
[7]*<500*
[8]*500 to <5,000*
[9]*5,000 to <10,000*
[10]*10,000 to <20,000*
[11]*20,000 to <30,000*

6.73 The net cost to the PBS/RPBS of tafamidis (effective price) was $100 million to <$200 million in Year 6 and a total of $500 million to <$600 million over 5.2 years.

6.74 The July 2020 submission estimated a net cost to the PBS/MBS for tafamidis (effective price) of $100 million to <$200 million in Year 6 and a total of $700 million to <$800 million over 6 years.

6.75 The estimated net cost of tafamidis was highly uncertain, and likely to be substantially underestimated overall, due to the following issues:

- The estimated eligible Australian population likely to be treated with tafamidis was based on the application of multiple factors with substantial cumulative uncertainty. Additionally, given that tafamidis would be the first disease-modifying agent listed for the treatment of ATTR-CM and is likely to increase awareness and diagnosis of the condition, along with increased usage of more accessible diagnostic methodology (especially radionucleide bone scintigraphy), it is likely that the utilisation and financial estimates will be higher than those presented in the resubmission.
- The resubmission estimated that diagnosis rates would increase from 30 to 80% over the first 6 years of listing. This was an assumption based on expert opinion that ATTR-CM is very underdiagnosed. It was unclear whether this estimate is likely to be accurate. The resubmission did not attempt to quantify current rates of diagnosis in Australia. The published estimates used to determine the prevalence of ATTR-CM may already account for the underdiagnosis of these patients.
- The proportion of patients with NYHA classes I-III appeared to be based on the complement of the proportion of patients with Gillmore stage III from an Australian study by Choi et al. 2020 (16%). Gillmore stage III is not equivalent to NYHA class IV. The proportion of patients with NYHA class IV was assumed to decline over time. Although it was not explicitly stated, this may be due to an assumption that the introduction of tafamidis will result in diagnosis at earlier NYHA classes, however no evidence was provided to support the estimates over time.
- The resubmission estimated the proportion of patients with non-persistent NYHA class III, based on the number of placebo treated patients in the ATTR-ACT trial (13/63; 21%) with NYHA class III at baseline who transitioned to NYHA class I-II by 6 months. Given the subjective nature of NYHA classification and the proposed restriction limiting treatment to NYHA class I and II (including patients with NYHA class III who return to NYHA class II with adequate management), it is likely that

the proportion of patients classified as non-persistent NYHA class III will be higher than estimated in the resubmission. The PSCR indicated that that the proportion could be 50%, based on the opinion of three clinical experts. The ESC considered this indicated substantial uncertainty regarding the proportion of patients with non-persistent NYHA class III in clinical practice.

- The resubmission assumed uptake rates of between 50 to 75% from years 1 to 6. No source nor justification for the uptake rates was provided in the resubmission.
- The resubmission assumed that listing would occur in November 2021, and therefore reduced the number of continuing patients to be 2/12 months of what they would be if treated for a full year. This significantly reduced the financial impact of year 1, and means that the utilisation and financial model does not cover 6 full years of listing, as required in the PBAC Guidelines (2016 v5.0).
- Whereas the economic model included the costs of screening patients with suspected ATTR-CM who are not eligible for tafamidis (it was assumed that 10.84 patients were screened for each treated tafamidis patient), the financial estimates only included the costs of screening associated with patients who are treated with tafamidis, and the costs of diagnostic testing were therefore likely to be significantly underestimated.

Quality Use of Medicines

6.76 The PSCR reiterated the sponsor's intention to support an ATTR-CM registry in Australia. The resubmission stated that the registry will enable the monitoring of overall survival and surrogate outcomes measures, and will provide further information on the condition as well as the treatment outcomes.

Financial Management – Risk Sharing Arrangements

6.77 In its consideration of the July 2020 tafamidis submission, the PBAC stated that a resubmission would need to include a risk sharing arrangement (RSA) that adequately addresses the uncertainties with the use of tafamidis in a broad population (para 7.19, Tafamidis PSD, July 2020 PBAC meeting). The resubmission presented alternative estimates of the eligible patient size, based on patients with NYHA class I/II or non-persistent NYHA class III symptoms at baseline, which the resubmission claimed have made the estimates more reliable. Although the sponsor proposed to enter an RSA with caps and rebates to manage uncertainty, details of a proposed RSA were not included in the resubmission, but the sponsor stated a willingness to work with the PBAC and PBAC Secretariat to develop a mutually acceptable agreement. The ESC and PBAC reiterated that an RSA would be required.

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

7 PBAC Outcome

7.1 The PBAC did not recommend tafamidis for the treatment of patients with transthyretin amyloid cardiomyopathy (ATTR-CM). The PBAC acknowledged again the high unmet need for treatments for this condition, and recognised that the resubmission had partially addressed a number of the PBAC's previous concerns. However, it considered that a further price reduction would be needed to reach an acceptable incremental cost-effectiveness ratio (ICER), and a Risk Sharing Arrangement (RSA) was needed to manage the high risk of use above the submission's estimates.

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 resubmission again positioned 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, histological confirmation of transthyretin precursor protein in cardiac tissue, and immunochemistry or mass spectrometry as required, with or without gene testing. The PBAC noted that standard management remained the appropriate comparator.

7.4 The PBAC recalled its previous position that the requested restriction should more closely align with the pivotal ATTR-ACT trial inclusion and exclusion criteria, and that specific discontinuation criteria should be included in the restriction (see Table 2). The PBAC considered that the resubmission had largely addressed these matters, noting two exceptions:

- The resubmission maintained that tafamidis should be able to be prescribed by not only specialist cardiologists, but also consultant physicians with experience in amyloid disorders. The PBAC considered this was acceptable, noting advice that ATTR-CM is currently diagnosed and treated in specialist amyloid centres, where consultant physicians may be managing these patients.
- The resubmission proposed to limit tafamidis eligibility to patients with NYHA class I and II heart failure on initiation (including patients with NYHA class III heart failure who return to NYHA class II with adequate management). Under the proposed restriction, patients with persistent NYHA class III would be ineligible to initiate tafamidis, but patients progressing to NYHA stage III whilst on treatment would be able to continue with PBS-subsidised therapy. The PBAC noted that this amendment to the patient population was proposed in an attempt to address its previous concern that the magnitude of the benefit of tafamidis with baseline NYHA class III was uncertain. However, the PBAC considered that the proportion of patients with non-persistent NYHA class III heart failure was uncertain.

7.5 The submission assumed <500 patients receiving non-PBS subsidised tafamidis would require grandfathering on to the PBS; restriction wording was not proposed. The PBAC considered that patients with Class I and II heart failure would be able to initiate via the proposed PBS restriction, although patients who had progressed from NYHA class II to NYHA class III heart failure during non-PBS-subsidised treatment would require a separate grandfathering restriction.

7.6 The PBAC recalled that it was previously concerned that the positive predictive value of bone scintigraphy may not be reproduced in non-specialist centres given that interpretation of bone scans is potentially subjective (paragraph 7.4, tafamidis PSD, July 2020 PBAC meeting). The PBAC considered that the resubmission had satisfactorily addressed this matter, as it presented expert opinion from a leading Australian nuclear medicine specialist stating that scans are able to be performed by all centres, and that reporting is now performed with standard criteria from consensus guidelines in Dorbala et al, 2019.

7.7 The PBAC recalled that it had previously accepted the clinical claim that tafamidis is superior in efficacy compared with standard management, but that the magnitude of benefit in the Australian PBS population was uncertain due to uncertain efficacy in patients with NYHA class III heart failure, the differences in baseline risk of death between NYHA classes and TTR genotypes, and the uncertain applicability of the ATTR-ACT population to the Australian setting in terms of the distribution of NYHA classes. It also recalled 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).

7.8 In response to these concerns, the resubmission amended the proposed PBS restriction in terms of NYHA classes (as noted above), and also presented additional clinical evidence. The previous submission was based on the ATTR-ACT trial and B3461045 long term extension study, and the resubmission presented new post hoc subgroup analyses of the ATTR-ACT trial, further interim results from the ongoing B3461045 study, and post hoc subgroup analyses of the combined ATTR-ACT and B3461045 data sets. In reviewing this new evidence, the PBAC's concerns regarding the magnitude of the benefit were lessened, and although a moderate amount of uncertainty remained, it recognised that tafamidis provided a substantial and clinically relevant improvement in efficacy overall. The PBAC:

- Recognised that limited data was available to assess the applicability of the ATTR-ACT trial to the Australian setting. Whilst the analyses presented were not indubitable (see paragraph 6.11), the PBAC considered that it may be reasonable to assume that the Australian PBS population would increasingly reflect the ATTR-ACT trial population as specific investigation for ATTR-CM becomes standard (per paragraph 6.13). However, it remained unclear whether cases diagnosed earlier would have more benign clinical courses and so the resubmission's claim that

earlier diagnosis would result in improvements in survival was not necessarily supported.

- Considered that the post hoc analyses with respect to NYHA class were difficult to interpret (paragraph 6.7 and 6.30). The PBAC remained of the view that the absolute benefit of tafamidis treatment will vary between subgroups, and that the higher rates of CV-related hospitalisation in NYHA class III patients treated with tafamidis versus placebo were not adequately explained by the resubmission. Nonetheless, the PBAC recognised that the exclusion of persistent class III patients from the listing partially mitigated this concern.
- Considered that the post hoc subgroups with respect to the 20 mg and 80 mg dose differences were also inconclusive and difficult to interpret (see paragraphs 6.33 and 6.34). However, the PBAC also acknowledged that the recommended dose in the TGA-approved Product Information (PI) is 61 mg once daily, with the PI noting that this is bioequivalent to 80 mg tafamidis meglumine.

7.9 The PBAC recalled that it previously considered that the clinical safety dataset was small and inadequate to make a claim of non-inferior safety compared to standard management (paragraph 7.11. tafamidis PSD, July 2020). The resubmission amended its claim to inferiority, which the PBAC considered reasonable, noting again that there were no significant toxicity or safety signals with tafamidis in the trial.

7.10 In terms of the economic analysis, the PBAC recollected that it considered the previous submission's estimate of cost-effectiveness to be unreliable given major structural limitations of the model and uncertain proportion of patients across NHYA classes (paragraph 7.15, tafamidis PSD, July 2020). The PBAC noted that the resubmission had adopted a new model (with structure and inputs described in paragraphs 6.47 to 6.51), intended to address PBAC's previous concerns (that is: patients remaining in baseline NYHA class; constant probability of CV hospitalisation; all CV hospitalisations non-fatal; and treatment effects maintained following treatment discontinuation). With regard to the resubmission's model, the PBAC noted that the base case ICER was $155,000 to <$255,000 per QALY after corrections made during evaluation, and that:

- The model still assumed maintenance of treatment effect following discontinuation. The pre-PBAC response attempted to account for discontinuation with a sensitivity analysis, which increased the ICER to $155,000 to <$255,000/QALY gained (using the corrected model), although the PBAC noted that this analysis did not fully correct the issue as the impact of treatment discontinuation on outcomes other than survival was not addressed (see paragraph 6.56).
- The model assumed constant transition probabilities beyond 30 months, with the consequence that probabilities for death from several health states in the later years of the model were lower than Australian general population estimates, which was not clinically plausible given the poor prognosis of ATTR-CM. The pre-

PBAC response conducted a sensitivity analysis to increase the risk of death by 5.3%, per six-month cycle from Year 4 onwards, which increased the ICER to $155,000 to < $255,000/QALY gained (using the corrected model). While this analysis represented a crude adjustment for mortality (see paragraph 6.53), the PBAC considered that it may be reasonable in the absence of better data.

- Combining the two sensitivity analyses in the pre-PBAC response resulted in an ICER of $155,000 to <$255,000 per QALY (using the corrected model). The PBAC considered that due to not addressing the impact of treatment discontinuation on all outcomes, this remained a likely underestimate.

7.11 Overall, the PBAC considered that the resubmission's model results were more reliable than those from the previous model, but that the ICER produced under the most realistic scenario presented ($155,000 to <$255,000 per QALY) remained excessively high. The PBAC noted that to achieve a more acceptable ICER of $75,000 to <$95,000 per QALY in this scenario, a further price reduction of 65% would be required. In the context of this substantial price reduction, the high clinical need, and clear effectiveness of medicine, the PBAC considered that the resubmission's model may provide a reliable basis for decision making.

7.12 Regarding the estimated PBS usage and financial implications, the PBAC noted that the resubmission's approach was extensively revised. The PBAC had considered that the previous financial implications were uncertain and likely underestimated and that given the very high financial impact ($700 million to <$800 million over 6 years), further work was required to determine the size of the eligible population in Australia, particularly the incidence and prevalence of the condition (paragraph 7.17, tafamidis PSD, July 2020). The resubmission used new data sources to estimate prevalence of ATTR-CM, revised diagnosis and uptake rates, used new sources to inform the distribution of patients across NYHA classes, and applied a reduced effective price for tafamidis. The PBAC considered that the 300 additional patients assumed to be grandfathered would be captured in the estimates of the prevalent population. The PBAC noted that the revised impact was $500 million to <$600 million over 5.2 years, but noting the issues in paragraph 6.75, agreed that the net cost likely remained underestimated. However, the PBAC considered that the resubmission's revised approach was appropriate in the context of these estimates being used to implement a RSA, and given the lack of more reliable alternative data on which to base the estimates.

7.13 The PBAC considered the outstanding issues may be addressed in a simple resubmission for tafamidis if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- An ICER of $75,000 to < $95,000/QALY for the model applying the two sensitivity analyses in the pre-PBAC response, noted in paragraph 7.10 (and corrected as per evaluation for errors in the calculation of acute disease costs and disease

management costs, and the inappropriate use of MBS benefit rather than MBS fee).

- Revised financial estimates accounting for a revised price, and costed over six full years, as required in the PBAC Guidelines (2016, v5.0), and excluding grandfathered patients as they are captured in the prevalent population.
- 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.

7.14 The PBAC also considered tafamidis addresses a high and urgent unmet clinical need and was expected to provide a substantial and clinically relevant improvement in efficacy, over any alternative therapies. Therefore, the PBAC considered an early resolution pathway would be acceptable if the resubmission addressed each of the points in the above paragraph with no further adjustment. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If any of these terms are not acceptable to the sponsor, a standard re-entry pathway is available.

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

Outcome:
Rejected

Addendum to the March 2021 PBAC Minutes:

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

8 Background

8.1 An early resolution resubmission was provided, which sought to address the PBAC's concerns from its March 2021 meeting, at which the Committee did not recommend tafamidis for the treatment of patients with transthyretin cardiac amyloidosis (ATTR-CM).

9 Consideration of the evidence

9.1 In March 2021 the PBAC "considered the outstanding issues may be addressed in a simple resubmission for tafamidis if the following changes were made, without any additional amendments to the economic evaluation or financial implications:

- An ICER of $75,000 to < $95,000 for the model applying the two sensitivity analyses in the pre-PBAC response, noted in paragraph 7.10 (and corrected as per evaluation for errors in the calculation of acute disease costs and disease management costs, and the inappropriate use of MBS benefit rather than MBS fee).
- Revised financial estimates accounting for a revised price, and costed over six full years, as required in the PBAC Guidelines (2016, v5.0), and excluding grandfathered patients as they are captured in the prevalent population.
- 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" (paragraph 7.13, tafamidis PSD, March 2021 PBAC meeting).

9.2 The table below summarises how each of these issues were addressed in the resubmission.

Table 18: Summary of key matters and how they were addressed in the current resubmission

PBAC advice (paragraph 7.13)	How the resubmission addressed this
An ICER of $[redacted][1] for the model applying the two sensitivity analyses in the pre-PBAC response	ICER of $[redacted][2]/QALY. [redacted]
Revised financial estimates accounting for a revised price, costed over six full years, and excluding grandfather patients.	The changes were made as requested.

PBAC advice (paragraph 7.13)	How the resubmission addressed this
	The total expenditure was estimated to be $[redacted][3] over 6 years, compared with $[redacted][4] over 5.2 years in the previous submission.
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	An RSA proposal was included, in which the proposed caps were higher than the resubmission's estimated financial expenditure (the proposed caps were $[redacted][3] over 6 years compared with the estimated expenditure of $[redacted][3]). A rebate of [redacted]% was proposed for any utilisation in excess of the caps.

Source: Compiled during preparation of the Minutes
The redacted values correspond to the following ranges:
[1]$75,000 to < $95,000
[2]$135,000 to < $155,000/QALY
[3]$200 million to < $300 million
[4]$500 million to < $600 million

9.3 A key additional change, not requested in Paragraph 7.13 of the previous PSD, would require patients with persistent class III heart failure to discontinue tafamidis. In the previous submission, while patients with persistent class III heart failure could not commence tafamidis, continuation was permitted until the patient progressed to class IV heart failure. This change resulted in significant changes to the economic model and financial estimates, namely additional health states in the economic model and additional assumptions in the financial estimates. As an early resolution resubmission, these changes were not evaluated.

9.4 The resubmission stated that the changes outlined in the table below had been made. As an early resolution resubmission, these changes were not evaluated.

Table 19: Summary of key differences between previous and current resubmission

Section	Previous resubmission	This resubmission
Section 1: Context		
Clinical issues addressed by the submission	Initiation in NYHA class I and II and non-persistent NYHA class III HF. Discontinuation in NYHA class IV HF.	Initiation in NYHA class I and II HF. Discontinuation in NYHA class III HF, confirmed by a further assessment after 3-6 months, and NYHA class IV HF.
Regulatory process		Includes a more complete list of international registrations.
Proposed PBS listing	Effective DPMQ of $[redacted]	Effective DPMQ of $[redacted]
	Initiation in NYHA class I and II and non-persistent NYHA class III HF. Discontinuation in NYHA class IV HF.	Initiation in NYHA class I and II HF. Discontinuation in NYHA class III HF, confirmed by a further assessment after 3-6 months, and NYHA class IV HF.
Section 2: Clinical evaluation		
Identify relevant trials		Literature searches updated. Further publications of ATTR-ACT and the LTE study identified.
Extended assessment of comparative harms		Literature search for extended safety updated. 6 publications identified.
		Updated to include results from latest periodic safety update report.

Section	Previous resubmission	This resubmission
Therapeutic conclusion		Therapeutic conclusion based on benefit of tafamidis in NYHA class I and II HF only.
Section 3: Economic evaluation		
Overall rationale of the economic evaluation	Initiation in NYHA class I and II and non-persistent NYHA class III HF. Discontinuation in NYHA class IV HF.	Initiation in NYHA class I and II HF. Discontinuation in NYHA class III HF, confirmed by a further assessment after 3-6 months, and NYHA class IV HF.
Literature review		Updated literature review performed. Two further publications discussed.
Section 4: Use of the medicine in practice		
Throughout Section 4	2021 first year of listing. 2026 sixth year of listing	2022 first year of listing. 2027 sixth year of listing.
Justification of the selected data sources	Initiation in NYHA class I and II and non-persistent NYHA class III HF. Discontinuation in NYHA class IV HF.	Initiation in NYHA class I and II HF. Discontinuation in NYHA class III HF, confirmed by a further assessment after 3-6 months, and NYHA class IV HF.
		Inclusion of population estimates for 2027.
Estimation of the use and financial impacts of the proposed medicine		Updated patient numbers according to revised years.
		Estimates include initiation in patients with NYHA class I-II only.
		Discontinuation includes patients who transition to NYHA class III and do not improve to class I-II during 3-6-month period.
		Revised pack numbers calculated.
		Revised financial impact according to other changes and with revised proposed effective prices.
		Revised financial impact according to other changes with revised proposed published prices.
Estimated financial implications for the PBS/RPBS		Changes to prescriptions and authorities in accordance with changes in years and reduced population.
		Changes in number of MBS items in accordance with changes in years and reduced population.
		Amendments to cost of procedures to 2021 values.
Identification, estimation and reduction of uncertainty		Revised sensitivity analyses included.
		Includes proposed risk share arrangement with caps and rebates.

Source: Table OV, pp xiii-xiv of the resubmission

10 PBAC Outcome

10.1 The PBAC did not recommend tafamidis for the treatment of patients with transthyretin amyloid cardiomyopathy (ATTR-CM). The PBAC considered that the changes made in the 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 ($135,000 to < $155,000/QALY) was significantly higher than the ICER requested ($75,000 to < $95,000/QALY) and noted that it relied on tafamidis being discontinued in patients with persistent class III heart failure. Further, 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.

10.2 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.

10.3 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 RSA expenditure caps, given the Committee had previously considered that the efficacy was uncertain in patients with NYHA class III heart failure (paragraph 7.7, tafamidis PSD, March 2021 PBAC meeting).

10.4 The PBAC reiterated that a resubmission for tafamidis should address the following issues which remain outstanding from paragraph 7.13 of the March 2021 PSD:

- An ICER of $75,000 to < $95,000for the model applying the two sensitivity analyses in the pre-PBAC response
- 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.

10.5 The PBAC noted that an early resolution pathway had been made available in March 2021, but considered that the remaining issues had not been resolved by the approach proposed in the sponsor's resubmission. The PBAC noted that any resubmission would be through the standard re-entry pathway.

Outcome:
Not recommended

11 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.

12 Sponsor's Comment

Pfizer is disappointed that the substantial changes proposed were not adequate to secure a positive recommendation from the PBAC to make tafamidis available for Australian patients with ATTR-CM