SMC2585

tafamidis 61mg soft capsules (Vyndaqel®)

Pfizer

06 October 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a second resubmission assessed under the end of life and orphan medicine process

tafamidis (Vyndaqel®) is accepted for use within NHSScotland.

Indication under review: for the treatment of wild-type and hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).

In a phase III study, 30 months of treatment with tafamidis (as meglumine) significantly reduced the risk of all-cause mortality and cardiovascular-related hospitalisation compared with placebo, in patients with wild-type or hereditary ATTR-CM.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tafamidis is a selective stabiliser of abnormal transthyretin (TTR); it acts by binding to TTR at the thyroxine binding sites, stabilising the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process.[1, 2] Tafamidis is the first medicine to be licensed for the treatment of transthyretin amyloidosis with cardiomyopathy (ATTR-CM).

The recommended dose is one capsule of tafamidis 61mg orally once daily. Tafamidis 61mg (free acid) corresponds to 80mg of the meglumine salt form of tafamidis. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis. [1]

A different formulation, tafamidis meglumine 20mg soft capsules, is licensed for the treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment but, in the absence of a submission, is not recommended for use by SMC (SMC877/13).[3]

1.2. Disease background

Transthyretin amyloidosis is a form of systemic amyloidosis resulting from the production of TTR proteins in the liver. These accumulate as amyloid deposits (amyloidosis) in tissues around the body, particularly the peripheral nerves (causing polyneuropathy) and the heart. The accumulation of TTR amyloid deposits in the heart results in ATTR-CM, a rare and fatal condition with most patients dying from cardiac causes, including sudden death, congestive heart failure and myocardial infarction. ATTR-CM can be wild-type when the TTR proteins become structurally unstable with age and this mainly occurs in older patients (usually >60 years, with a reported average age of onset of 75 years), affects more men than women and median survival is estimated to be around 3.6 years. ATTR-CM can also be hereditary (also referred to as variant ATTR-CM), caused by one of 120 mutations in the TTR gene, such as Val122Ile and Leu111Met. Patients with hereditary disease are generally younger than those with wild-type disease but age varies with the mutation (age of onset reported as varying between 30 and 80 years old dependent on the mutation) and the median survival is thought to be lower, around 25.6 months. ATTR-CM causes the heart to stiffen resulting in heart failure symptoms. It is has recently been considered that 10 to 15% of older adults with heart failure may have undiagnosed wild-type ATTR-CM.[2, 4]

1.3. Treatment pathway and relevant comparators

No other medicines are specifically licensed for the treatment of ATTR-CM. Patients are generally managed with treatments used for heart failure, including diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers and second generation calcium channel blockers. For some patients, cardiac and/or liver transplant might be an option. However, given the generally advanced age of patients with ATTR-CM at diagnosis, and their co-morbid burden of illness, transplantation is rarely an option. [2]

Clinical experts consulted by SMC considered that tafamidis would not displace any treatments but would be used in addition to current standard of care (with supportive care and eventually palliative care or transplant in eligible patients).

1.4. Category for decision-making process

Eligibility for interim acceptance decision option
Tafamidis received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency.

Eligibility for a PACE meeting
Tafamidis meets SMC end of life and orphan criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of tafamidis comes from the ATTR-ACT study. Details are summarised in Table 2.1.

Table 2.1. Overview of relevant study [1, 2, 5]

Criteria	ATTR-ACT
Study design	Multicentre, randomised, double-blind, phase III study
Eligible patients	• Patients aged 18 to 90 years • Hereditary ATTR-CM with TTR genotyping or wild-type ATTR-CM with presence of TTR precursor protein confirmed by immunohistochemistry, scintigraphy or mass spectrometry • Presence of amyloid deposits in biopsy specimens obtained from cardiac or non-cardiac sites (with biopsy done at screening or documented as having been performed previously) • Evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12mm • History of heart failure evidenced by at least one prior hospitalisation for heart failure or clinical evidence of heart failure (without hospitalisation) manifested by signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with diuretics • A 6-minute walk test (6MWT) of >100 metres • A plasma N-terminal pro-B-type natriuretic peptide concentration ≥600 picograms/mL
Treatments	Eligible patients were randomised in a ratio of 2:1:2 to receive tafamidis meglumine 80mg (n=176), tafamidis meglumine 20mg (n=88) or placebo (n=177) orally once daily for 30 months. Patients continued to take standard treatment during the study period but were not allowed to take non-steroidal anti-inflammatory drugs, tauroursodeoxycholate, doxycycline, diflunisal, calcium-channel blockers or digitalis.
Randomisation	Randomisation was stratified by TTR status (variant or wild-type) and baseline New York Heart Association (NYHA) class (I and II or III) and region (US or non-US).
Primary outcome	The primary outcome was a hierarchical combination of “all-cause mortality” and the frequency of cardiovascular (CV)-related hospitalisations during the study. All-cause mortality was a composite of all-cause mortality, heart transplantation or the implantation of a cardiac mechanical assist device. The primary analysis compared the pooled group of patients who received tafamidis meglumine (80mg and 20mg) with placebo using the Finkelstein-Schoenfeld method which recognises the higher importance of all-cause mortality. It compared each patient

	with every other patient in each stratum in a pair-wise manner that proceeds in a hierarchical fashion using all-cause mortality followed by frequency of CV-related hospitalisations when patients cannot be differentiated based on mortality, reported as a win ratio (number of pairs of tafamidis-treated patient wins/number of pairs of placebo-treated patient wins). The primary analysis was performed in the intention-to-treat (ITT) population, which included all randomised patients who received at least one dose of study treatment and had one post baseline assessment.
Secondary outcomes	Key secondary outcomes: 6MWT and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score. Other secondary outcomes included: CV-related mortality, frequency of CV-related hospitalisation and all-cause mortality.
Statistical analysis	A hierarchical statistical testing strategy was applied to the two key secondary outcomes 6MWT and Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Other secondary outcomes were not adjusted for multiplicity, thus results are considered descriptive only and non-inferential (no p-values reported).
6MWT=6 minute walk test; LS=least square; ATTR-CM= transthyretin amyloidosis with cardiomyopathy; CI= confidence interval; CV= cardiovascular; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire-Overall Summary; NYHA= New York Heart Association; TTR= abnormal transthyretin	

Tafamidis meglumine (pooled dose groups) significantly reduced the risk of all-cause mortality and CV-related hospitalisation compared with placebo over the 30-month study period. There were also significantly less declines in 6MWT and KCCQ-OS score in tafamidis meglumine treated patients compared with placebo-treated patients. Details are presented in Table 2.2 below.[1, 2, 5, 6]

Table 2.2: Results for the primary and secondary outcomes of the ATTR-ACT study in the ITT population [1, 2, 5, 6]

	Tafamidis meglumine pooled (n=264)	Placebo (n=177)
Primary outcome		
Patients alive at 30 months, % (n/N)	70% (186/264)	57% (101/177)
Average CV-related hospitalisations during 30 months among those alive at 30 months, per patient per year	0.30	0.46
Win ratio (95% CI)[AB]	1.70 (1.26 to 2.29), p<0.001	
Key secondary outcomes		
6MWT at baseline, metres	350.6	353.3
LS mean change in 6MWT at 30 months, metres	-54.9	-130.6
LS mean difference (95% CI)	75.7 (57.6 to 93.8), p<0.001	
KCCQ-OS at baseline	67.3	65.9
LS mean change in KCCQ-OS at 30 months	-7.2	-20.8
LS mean difference (95% CI)	13.6 (9.5 to 17.8), p<0.001	
Other secondary outcomes		
CV-related mortality[B]	24% (64/264)	36% (63/177)
Hazard ratio (95% CI)	0.69 (0.49 to 0.98)	
CV-related hospitalisations	52% (138/264)	60% (107/177)
CV-related hospitalisations per year[C]	0.475	0.702
Relative risk ratio (95% CI)	0.68 (0.56 to 0.81)	
All-cause mortality[B]	30% (78/264)	43% (76/177)
Hazard ratio (95% CI)[D]	0.70 (0.51 to 0.96)	

[A] using Finkelstein-Schoenfeld analysis, a win represents a patient doing better based on the hierarchical comparison.
[B] heart transplantation and implantation of cardiac mechanical assist device were considered indicators for reaching end-stage and these were treated as equivalent to death.
[C] using Poisson regression analysis.
[D] using Cox regression analysis.
6MWT=6 minute walk test; LS=least square; CI= confidence interval; CV= cardiovascular; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire-Overall Summary

Pre-specified subgroup analyses generally found consistent results favouring tafamidis meglumine over placebo. However, there seems to be some differences in some subgroups as summarised in the Table 2.3 below.

Table 2.3: Results of subgroup analyses for the components of the primary outcome of the ATTR-ACT study [7-9]

	Treatment effect: tafamidis meglumine pooled versus placebo	
Subgroup of interest	**All-cause mortality (hazard ratio [95% CI])**	**CV-related hospitalisation (risk ratio [95% CI])**
Hereditary ATTR (n=106)	0.69 (0.41 to 1.17)	0.94 (0.66 to 1.34)
Wild type ATTR (n=335)	0.71 (0.47 to 1.05)	0.61 (0.49 to 0.75)
NYHA class I or II (n=300)	0.57 (0.36 to 0.90)	*
NYHA class III (n=141)	0.84 (0.54 to 1.30)	1.41 (1.05 to 1.90)

ATTR-CM= transthyretin amyloidosis with cardiomyopathy; CI= confidence interval; CV= cardiovascular; NYHA= New York Heart Association
**results considered confidential by the company*.

2.2. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed using the key secondary outcome KCCQ-OS score, as detailed in Table 2.2 above, and the generic instrument EuroQoL-5Dimensions 3-Level (EQ-5D-3L) index score and visual analogue scale (VAS), as exploratory outcomes. *The results remain confidential*.[7]

*Other data were also assessed but remain confidential.**

2.3. Supportive study

The 30-month ATTR-ACT study was followed by an ongoing, open-label extension study in which patients who completed the tafamidis meglumine groups of ATTR-ACT, continued to receive the same dose of open-label tafamidis meglumine (continuous tafamidis). All patients who completed the placebo group were re-randomised in a 2:1 ratio to receive open-label tafamidis meglumine 80mg or 20mg orally once daily (placebo to tafamidis group). Following a protocol amendment in July 2018, where possible all patients transitioned to the new free acid formulation of tafamidis 61mg (similar to tafamidis meglumine 80mg). Study treatment was continued for up to 60 months. The primary efficacy outcome was all-cause mortality which as in ATTR-ACT classified heart transplant or insertion of a cardiac assist mechanical device as death. [10]

At the August 2021 cut-off date, in patients with NYHA class I/II symptoms at baseline, all-cause mortality was lower in the continuous tafamidis group than in the placebo to tafamidis group with a hazard ratio (HR) of 0.50 (95% confidence interval [CI]: 0.35–0.73; continuous tafamidis n=121;

placebo to tafamidis n=114; median follow-up of 61 and 60 months, respectively). In patients with NYHA class III symptoms at baseline, all-cause mortality was also lower in the continuous tafamidis group when compared with the placebo to tafamidis group but with a higher HR of 0.64 (95% CI 0.41–0.99; continuous tafamidis n=55; placebo to tafamidis n=63; median follow-up: 60 and 56 months, respectively). [11]

3. Summary of Safety Evidence

Tafamidis meglumine was generally well tolerated during the ATTR-CM study with a safety profile similar to placebo.[2]

In the 30-month ATTR-ACT study, any treatment-emergent adverse event (AE) was reported by 95% (167/176) of patients in the tafamidis meglumine 80mg group, 99% (87/88) of patients in the tafamidis meglumine 20mg group and 97% (172/177) in the placebo group and these were considered treatment-related in 45%, 39% and 51% respectively. In the tafamidis meglumine 80mg and 20mg and placebo groups respectively, patients with a reported serious AE were 53%, 53% and 59%, and patients discontinuing therapy due to an AE was 23%, 18% and 29%.[2]

The most frequently reported treatment-emergent AEs of any grade with an incidence in the tafamidis meglumine 80mg and 20mg and placebo groups respectively were: cardiac failure (26%, 34% and 34%), fall (24%, 31% and 23%), dyspnoea (16%, 24% and 31%), atrial fibrillation (20%, 18% and 19%), constipation (15%, 16% and 17%), diarrhoea (12%, 11% and 22%), nausea (11%, 10% and 20%), asthenia (10%, 12%, and 6.2%), fatigue (16%, 18% and 19%), peripheral oedema (17%, 19% and 18%), bronchitis (12%, 10% and 11%) and pneumonia (13%, 11% and 9.6%). The most frequently reported treatment-related AEs were diarrhoea (8.0%, 2.3% and 10%), nausea (5.7%, 1.1% and 5.6%) and urinary tract infection (2.3%, 5.7% and 4.5%).[2]

There were no treatment-related deaths during the ATTR-ACT study.[2]

4. Summary of Clinical Effectiveness Considerations

The key strengths and uncertainties of the clinical case are summarised below.

4.1. Key strengths

- In the key study, the primary composite outcome of all-cause mortality and CV-related hospitalisation significantly favoured tafamidis meglumine over placebo, which regulators considered of main importance. The win ratio for the primary analysis (1.70) indicated that tafamidis meglumine was associated with a 70% higher chance of having a better outcome based on a hierarchical combination of all-cause mortality and CV-related hospitalisation compared with placebo. [2]
- Key secondary outcomes, which assessed walking function and quality of life, were supportive; although regulators noted that the magnitude of effect was more difficult to appreciate with these outcomes. [2]
- The components of the primary outcome also descriptively favoured tafamidis meglumine over placebo. [2, 5]

4.2. Key uncertainties

- A difference between treatment groups was only evident after 16 to 18 months of study treatment. The controlled treatment continued for a further 12 months, to 30 months, and further longer term controlled data are lacking.
- ATTR-ACT was not powered for subgroup analyses and results should therefore be treated with caution. Pre-specified subgroup analyses generally found consistent results favouring tafamidis meglumine over placebo according to wild type or hereditary disease, tafamidis meglumine dose and NYHA class; however there seems to be some differences in some subgroups.
    - The treatment effect favoured tafamidis meglumine in both wild-type and hereditary disease; but the treatment effect on CV-related hospitalisation was small in patients with hereditary ATTR-CM. There was a tendency to higher clinical events and lower TTR stabilisation in the hereditary subgroup, compared to the wild-type subgroup. Patients with hereditary ATTR-CM may have more severe disease and in practice, the medical need and management of these patients may differ from those with wild-type disease. For this reason, the Summary of Product Characteristics (SPC) recommends TTR genotyping as an assessment tool for diagnosis.[1, 2]
    - In the subgroup of patients with NYHA class III disease, the relative risk of CV-related hospitalisation was higher with tafamidis meglumine compared with placebo, although all-cause mortality and key secondary outcomes favoured tafamidis meglumine. Regulators noted that in patients with NYHA class III, the rates of CV-related hospitalisations were 77% in the tafamidis meglumine patients and 59% in placebo patients and that CV-related mortality also tended to be higher (51% versus 49%, respectively). In this context, the SPC notes that tafamidis should be started as early as possible in the disease course when the clinical benefit on disease progression could be more evident. Conversely, when amyloid-related cardiac damage is more advanced, such as in NYHA class III, the decision to start or maintain treatment should be taken at the discretion of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy.[1, 2]
- ATTR-ACT excluded patients with NYHA class IV disease and the treatment effects are therefore not known in these patients. Although the marketing authorisation does not restrict by NYHA class, the SPC notes that there are limited data in patients with NYHA class IV.[1, 2]
- In addition <10% of study patients had NYHA class I, reflecting the difficulty in diagnosing ATTR-CM in patients with no symptoms of heart failure. Regulators noted there is a risk of misuse in the elderly in the absence of clear diagnosis of ATTR-CM in patients without symptoms and the SPC states that ATTR-CM must be appropriately confirmed before starting tafamidis.[1, 2]
- The study was not designed or powered to compare the two doses of tafamidis meglumine with placebo and so no conclusions can be drawn. The submitting company did not seek marketing authorisation for ATTR-CM using the 20mg dose of tafamidis meglumine. The tafamidis meglumine 80mg dose group provided the largest evidence base and tolerability was similar with both dosing groups.

- The ATTR-ACT study used tafamidis meglumine (80mg or 20mg) which differs to the new free acid formulation, tafamidis 61mg which is licensed for use in patients with ATTR-CM. It has been shown that 61mg tafamidis free acid is similar to 80mg tafamidis meglumine but bioequivalence has not strictly been proven. The new formulation has only been assessed in short-term pharmacokinetic/ pharmacodynamics studies and the ATTR-ACT extension study. The submitting company reports that this formulation was developed to aid compliance in an elderly patient population but the dosing of a single 61mg tafamidis capsule does not allow the option to reduce the dose if adverse events develop. However, regulators noted that both doses of tafamidis meglumine assessed in ATTR-CM were relatively well tolerated.[1, 2]

4.3. Ongoing studies

Ongoing studies including ATTR-ACT open-label extension study are unlikely to address the uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that tafamidis fills an unmet need in this therapeutic area as there are no effective treatments for ATTR-CM. In addition, they considered that it is a therapeutic advancement as the first specific treatment for this condition; and they suggested that the place in therapy of tafamidis would be for earlier disease stages.

4.5. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on the service delivery as additional follow-up may be needed.

5. Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of tafamidis, as an orphan and end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- ATTR-CM is a gradually progressive and ultimately fatal cause of heart failure. Patients typically suffer symptoms of heart failure and develop difficulties in daily activities, which as the disease progresses, makes them more dependent on relatives or carers. The physical and psychological burden of the disease has a huge negative impact of patients' quality of life.
- There are currently no other specific medicines licensed for the treatment of ATTR-CM and management is supportive to control symptoms. There is a significant unmet need for an effective and well tolerated treatment that can alter the course of the disease.

- Tafamidis is the first disease modifying treatment for ATTR-CM and has been shown to slow the rate of disease progression. It may reduce the symptoms of heart failure, reduce the frequency of hospital admissions and the risk of death due to ATTR-CM.
- Tafamidis offers patients the hope of an effective treatment and may allow them to remain independent and maintain normal living for longer by slowing the decline in exercise capacity and in quality of life.

It is generally well tolerated and is a once a day oral treatment which is manageable for patients and families/carers.

Additional Patient and Carer Involvement

We received a joint patient group submission from the UK ATTR Amyloidosis Patients' Association (UKAPTA) and Cardiomyopathy UK, which are both registered charities. UKAPTA has received 30% pharmaceutical company funding in the past two years, including from the submitting company. Cardiomyopathy UK has received 13.4% pharmaceutical company funding in the past two years, including from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their joint submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary description of the economic analysis performed is provided in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost utility analysis
Time horizon	Lifetime (25 years based on an assumed starting age of 74)
Population	Adult ATTR-CM (Wild-type or Variant genotype) patients with baseline NYHA class I-III. This matched the population included in the central clinical study, ATTR-ACT, but was narrower than the licence population.
Comparators	Tafamidis plus best supportive care (BSC) was compared with BSC alone. BSC included diuretics, anticoagulants, antiplatelet agents, lipid lowering agents, beta blockers, angiotensin-converting-enzyme (ACE) inhibitors and renin-angiotensin-aldosterone system (RAAS) inhibitors.
Model description	A five state Markov model was used. Four of the included states were defined based on NYHA functional classifications (Stages I-IV), with an additional death state.
Clinical data	Clinical inputs were based on individual patient-level data from ATTR-ACT and the ATTR-ACT extension studies. Within the ATTR-ACT study, tafamidis meglumine was administered at 20mg or 80mg doses. These data were pooled and assumed representative of patients receiving a 61mg dose of tafamidis plus BSC. The placebo arm of the ATTR-ACT study was used as a proxy for the BSC arm of the economic model.
Extrapolation	Transitions between NYHA class states was evaluated at six-month intervals. Five transitions (up to 30 months) were estimated directly from the ATTR-ACT data. In the absence of observed data, for transitions taking place after 30 months a singular transition matrix is employed, with transition rates derived by fitting a smoothed multinomial distribution to all transitions observed during the within-trial phase of ATTR-ACT.

	Available data from the ATTR-ACT long-term extension study were used to inform survival extrapolations. This looked to account for the excess mortality of ATTR-CM patients and the variability in mortality between NYHA class states.
Quality of life	Health state utility values, were informed via analysis of EuroQoL-5-Dimensions 3- Level (EQ-5D-3L) data collected during ATTR-ACT study. In the base case these were independent of treatment received. Disutilities of AEs and CV-related hospitalisations were not included.
Costs and resource use	Medicine costs included acquisition costs for tafamidis and the component medicines of BSC. Administration costs for all treatments were assumed as zero. Within the model, patients received BSC for the duration of their lives, but tafamidis was discontinued based on time on treatment data observed in the ATTR-ACT and ATTR-ACT extension studies. The company also assumed that patients in the NYHA IV state would cease tafamidis treatment. Other costs included were cardiology outpatient visits, echocardiograms, and community nurse visits, CV-related hospitalisation costs, AEs and end of life costs.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price of tafamidis. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results.

6.2. Results

Compared to BSC, tafamidis plus BSC was estimated to generate additional quality adjusted life years (QALYs), but at a positive incremental costs. The increase in QALYs was mainly driven by greater occupancy of the NYHA II health state in the tafamidis plus BSC arm. The key driver of cost differences was the acquisition cost of tafamidis.

The details of the economic results, using both PAS-discounted and list price for tafamidis, have been listed as commercial in confidence by the submitting company.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

A variety of sensitivity and scenario analyses were performed to explore areas of uncertainty.

Sensitivity analysis suggested that the length of the modelled time horizon, health state utility values, CV-related hospitalisation rates and age were key drivers of the economic results.

Scenario analysis also showed that assumptions relating to the stopping rule, the extrapolation of overall survival and the time horizon had a large impact on the incremental cost effectiveness ratio.

*Other data were also assessed but remain confidential.**

6.4. Key strengths

Key strengths of the economic analysis are as follows:

- The included comparator of BSC alone was appropriate in the absence of other treatment options.
- The model structure, which used a Markov model and health states defined by NYHA class, was appropriate to reflect the condition.

- Direct head-to-head evidence from ATTR-ACT, as well as new long-term evidence from the ATTR-ACT extension study, were applied in the economic model and aligned with the clinical evidence presented.
- Utility values applied in the economic analysis were directly available from EQ-5D-3L data collected in the ATTR-ACT study. Comparisons between the values estimated from the ATTR-ACT study and utility values identified in the literature suggested that the model input values were not subject to treatment bias and had face validity.

6.5. Key uncertainties

Key uncertainties relating to the economic analysis are as follows:

- In the tafamidis plus BSC arm, a stopping rule was applied to patients entering NYHA class IV, as a proxy for end-stage heart failure. Clinical experts consulted by SMC suggested that this was not appropriate or feasible in clinical practice. Therefore, the long-term treatment costs of tafamidis may have been underestimated. A scenario removing the stopping rule increased the incremental cost-effectiveness ratio.
- The economic model had a monthly cycle length, but only modelled transitions between NYHA class states every 6 months. This schedule of movements may not reflect clinical practice assessments.
- The use of a single extrapolation matrix, derived from the total 30 month trial observation period, to model all subsequent transitions assumes no change in the effectiveness of tafamidis over time. That has not been demonstrated and remained a source of uncertainty.
- Clinical benefit of tafamidis is assumed to continue for patients who discontinue tafamidis, hence patients could move into less severe NYHA health states without accruing costs of active treatment. The company justify this based on the data utilised to estimating long-term outcomes including both patients on tafamidis and those who have discontinued, but this remains an area of uncertainty.

7. Conclusion

The Committee considered the benefits of tafamidis in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that a number of the criteria were satisfied: a substantial improvement in life expectancy in the patient population targeted in the submission, a substantial improvement in quality of life and the absence of other treatments of proven benefit. In addition, as tafamidis is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, and after application of the appropriate SMC modifiers, the Committee accepted tafamidis for use in NHSScotland.

8. Guidelines and Protocols

Relevant guidelines include:

- 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. [12]

9. Additional Information

9.1. Product availability date

17 July 2020

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
tafamidis	**61mg orally once daily**	**129,645**

Costs from BNF online on 04 August 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines or PAS associated with medicines used in a combination regimen.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 14 September 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These

contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.