Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2426

tafamidis 61mg soft capsules (Vyndaqel®)

Pfizer Limited

05 November 2021

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 resubmission assessed under the orphan and end of life medicine process

tafamidis (Vyndaqel®) is not recommended 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.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

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

Chairman
Scottish Medicines Consortium

Indication

For the treatment of wild-type and hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM).[1]

Dosing Information

Tafamidis 61mg orally once daily. The soft capsules should be swallowed whole and not crushed or cut. Tafamidis may be taken with or without food. Tafamidis 61mg corresponds to 80mg of tafamidis meglumine. Tafamidis and tafamidis meglumine are not interchangeable on a per mg basis.

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 New York Heart Association (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. There are limited clinical data in patients with NYHA class IV.

Treatment should be initiated under the supervision of a physician knowledgeable in the management of patients with amyloidosis or cardiomyopathy.[1]

Product availability date

18 February 2020

Tafamidis received a positive scientific opinion under the Early Access to Medicines Scheme with the Medicines and Healthcare Products Regulatory Agency on 24 May 2019.

EMA orphan designations for tafamidis for hereditary ATTR-CM (orphan designation EU/3/06/401 granted on 28 August 2006) and for wild-type ATTR-CM (orphan designation EU/3/12/1066 granted on 11 August 2012) were maintained at marketing authorisation.[2, 3]

Tafamidis meets SMC orphan and end of life criteria for this indication.

Summary of evidence on comparative efficacy

Transthyretin amyloidosis (ATTR) is a form of systemic amyloidosis resulting from the production of abnormal transthyretin (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 transthyretin amyloid cardiomyopathy (ATTR-CM) and can lead to diastolic dysfunction progressing to restrictive cardiomyopathy and heart failure. Tafamidis is a selective stabiliser of TTR which 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] A different formulation, tafamidis meglumine 20mg soft capsules (Vyndaqel®), is licensed for the

treatment of transthyretin amyloidosis in adult patients with stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment but has not been recommended for use by SMC (SMC877/13).[4]

The evidence for tafamidis to treat ATTR-CM comes from a multicentre, randomised, double-blind, phase III study (ATTR-ACT) which evaluated the efficacy and safety of the salt formulation, tafamidis meglumine, versus placebo in 441 patients with ATTR-CM. Note the formulation of tafamidis used in ATTR-CM was tafamidis meglumine 80mg, which corresponds to 61mg of the new free acid formulation. Eligible patients were aged 18 to 90 years with hereditary ATTR-CM (confirmed by amyloid deposits on biopsy from cardiac or non-cardiac sites) or wild-type ATTR-CM (confirmed by transthyretin precursor protein on immunohistochemical analysis, scintigraphy or mass spectrometry). They had evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm; history of heart failure evidenced by at least one prior hospitalisation for heart failure or clinical evidence of heart failure manifested in signs or symptoms of volume overload or elevated intracardiac pressures requiring treatment with diuretics; 6-minute walk test (6MWT) of >100 metres and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥600 picograms/mL. 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. Randomisation was stratified by TTR status (variant or wild-type) and baseline NYHA class (I and II or III) and region (US or non-US). 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.[2, 5]

The primary outcome was a hierarchical combination of "all-cause mortality" and the frequency of cardiovascular-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 patient 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 cardiovascular-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. 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 included cardiovascular-related mortality, frequency of cardiovascular-related hospitalisation and all-cause mortality and since these were not adjusted for multiplicity, results are considered descriptive only and non-inferential (no p-values reported).[1, 2, 5]

Tafamidis meglumine (pooled dose groups) significantly reduced the risk of all-cause mortality and cardiovascular-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. Other secondary outcomes also favoured tafamidis meglumine over placebo. Details are presented in Table 1 below.

Table 1: Results for the primary and secondary outcome of the ATTR-ACT study in the ITT population

	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		
Cardiovascular-related mortality[B]	24% (64/264)	36% (63/177)
Hazard ratio (95% CI)	0.69 (0.49 to 0.98)	
Cardiovascular-related hospitalisations	52% (138/264)	60% (107/177)
Rate of cardiovascular-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; KCCQ-OS= Kansas City Cardiomyopathy Questionnaire-Overall Summary

Health Related Quality of Life (HRQoL) was assessed using the key secondary outcome KCCQ-OS score, as detailed in Table 1 above and the generic instrument EuroQoL-5Dimensions, 3-Level (EQ-5D-3L) index score and visual analogue scale (VAS) as exploratory outcomes.[6]

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. 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. 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. Interim results, at cut-off date August 2019, found that 43% (75/176) of patients who received tafamidis meglumine 80mg and then tafamidis 61mg (median treatment duration of 51.9 months) and 61% (108/177) of patients who received placebo and then tafamidis (median treatment duration of 51.4 months) had died. Estimated Kaplan Meier median survival was not estimable in the tafamidis 80mg/61mg group and 35.8 months in the placebo/tafamidis group.[7]

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

Summary of evidence on comparative safety

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]

Summary of clinical effectiveness issues

Transthyretin amyloid cardiomyopathy (ATTR-CM) is 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), affects more men than women and median survival is estimated to be around 3.6 years. ATTR-CM can also be hereditary, 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 and the median survival is thought to be lower, around 25.6 months.[2, 8] ATTR-CM causes the heart to stiffen resulting in heart failure symptoms and treatment is generally supportive including medication used for heart failure. However, many standard heart failure medicines are not useful in patients with cardiac amyloidosis and fluid balance is considered important through restricting fluid and salt intake and the use of diuretics. It is has recently been considered that 10 to 15% of older adults with heart failure may have undiagnosed ATTR-CM. Earlier diagnosis and treatment to slow or stop progression of ATTR-CM may offer the best treatment option but patients require specific assessments and diagnosis before starting appropriate treatment.[8] The National Amyloidosis Centre in London provides a diagnostic, staging, monitoring and management advisory service for patients with amyloidosis in the UK. Tafamidis is the first medicine to be licensed for the treatment of ATTR-CM. Tafamidis meets SMC orphan and end of life criteria for the treatment of ATTR-CM. 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.

Evidence from the ATTR-ACT study found that the primary composite outcome of all-cause mortality and cardiovascular-related hospitalisation significantly favoured tafamidis meglumine over placebo in the ITT population according to the Finkelstein-Schoenfeld method. The win ratio for the primary analysis (1.70) indicated that tafamidis meglumine was associated with a higher chance of having a better outcome based on a hierarchical combination of all-cause mortality and cardiovascular-related hospitalisation compared with placebo. This was supported by results of the key secondary outcomes: 6MWT (difference of 75.7 metres versus placebo) and KCCQ-OS score (difference of 13.6 points versus placebo). The components of the primary outcome (all-cause mortality and cardiovascular-related hospitalisation) also favoured tafamidis meglumine over placebo. However, these were analysed separately as secondary outcomes but were not included in the hierarchical testing strategy, so results were descriptive only. Treatment with tafamidis meglumine resulted in fewer deaths than treatment with placebo (30% versus 43%; absolute difference of 13%). The incidence of cardiovascular-related hospitalisations per year was reduced from 0.702 in the placebo group to 0.475 in the tafamidis meglumine group.[2, 5]

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.

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. ATTR-ACT was not powered for subgroup analyses and results should therefore be treated with caution. The treatment effect favoured tafamidis meglumine in both wild-type and hereditary disease but the treatment effect on cardiovascular-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 cardiovascular-related hospitalisation was higher in the tafamidis meglumine group compared with the placebo group, although all-cause mortality and key secondary outcomes favoured tafamidis meglumine. The European Product Assessment Report (EPAR) notes that in patients with NYHA class III, the rates of cardiovascular-related hospitalisations were 80% in the tafamidis meglumine patients and 59% in placebo patients and that cardiovascular-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. 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. The EPAR notes 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. However the EPAR notes that there was a trend in higher favourable effect with tafamidis meglumine 20mg dose group compared with 80mg dose group for all clinical outcomes including all-cause mortality (27% versus 31%), cardiovascular-related hospitalisation (48% versus 54%) and cardiovascular-related mortality (22% versus 26%). A higher favourable effect with the 80mg dose compared with the 20mg was only noted from post hoc exploratory analyses on the reduction of NT-proBNP and troponin I at 30 months. The 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. The SPC and EPAR note that the bioequivalence of these formulations is similar but 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 company report 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, the EMA noted that both doses of tafamidis meglumine assessed in ATTR-CM were relatively well tolerated.[1, 2]

The introduction of tafamidis would offer the first licensed treatment for patients with hereditary or wild-type ATTR-CM. Clinical experts consulted by SMC considered that tafamidis offered a therapeutic advancement as the first specific treatment for this condition.

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. Frequent hospital admissions may be required. 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. This could delay the need for support and reduce the burden of the disease on the patients' carers and relatives.
- It is a generally well tolerated, 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 90% pharmaceutical company funding in the past two years, with none from the submitting company. Cardiomyopathy UK has received 10.4% 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 submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating the use of tafamidis within its full licensed indication. The analysis compared tafamidis with best supportive care, which comprised a variety of therapeutic classes including diuretics, anticoagulants, angiotensin-converting enzyme (ACE) and renin-angiotensin-aldosterone system (RAAS) inhibitors and beta-

blockers. Clinical experts stated that best supportive care represents the most appropriate comparator.

A discrete time, cohort-level Markov model was used to represent four distinct health states (NYHA class I – NYHA class IV), alongside an absorbing health state of death. Additional sub-states were used to represent treatment discontinuation for tafamidis-treated patients, and cardiovascular-related hospitalisations. Patients entered the model distributed across NYHA classes I – III according to the proportions observed within the ATTR-ACT study, and from this point could transition between the NYHA classes at six-monthly intervals. A shorter cycle length of one-month was used to model the occurrence of death, hospitalisation and treatment discontinuation. A fifty-five year time horizon was used, although the mean age within the model was limited to a maximum of 101 years.

Transitions between NYHA classes within the first 30 months of the model were based upon treatment-specific transition-probabilities derived at six-monthly intervals from the ATTR-ACT study (pooled tafamidis arms and placebo arm).[5] Following this point, a single extrapolative matrix was used for each treatment, making use of the summed probabilities of movement between each class over the 30-month study observation period. Overall survival was derived by estimating the total hazard of death, by summing the background mortality for a Scottish population and the extrapolated excess hazard of death, utilising independently-fitted log-normal distribution for tafamidis and generalised gamma distribution for BSC. The mortality hazards were then disaggregated by NYHA class, by applying a risk ratio derived using a Cox proportional hazards model stratified by NYHA class at month 30 of ATTR-ACT. Monthly risk of cardiac hospitalisation was estimated based on the observed NYHA-class-specific and treatment-specific rates observed within the same study. Following discontinuation of tafamidis (which is discussed further below), patients were assumed to retain the same clinical benefits of tafamidis in terms of NYHA transition probabilities, overall survival and cardiac hospitalisation as patients who remain on treatment.

EQ-5D-3L data were collected within the ATTR-ACT study and valued using standard methods.[9] Utilities were applied on a treatment-specific basis across the classes. No disutilities were applied for adverse events or cardiac hospitalisation, and age-adjustment was not performed.

Medicines costs included the acquisition cost of tafamidis and concomitant medications, as well as a one-off cost of adverse events applied at model entry. This resubmission has been assessed under the fast track resubmission process. 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.

Treatment discontinuation for tafamidis was assumed to occur in two ways: a time-to-event analysis was applied to extrapolate the estimated probability of treatment discontinuation over the time horizon (using an exponential model). In addition, a stopping rule was applied at the point of transition to NYHA class IV (as a proxy for the occurrence of end-stage heart failure). Patients were assumed to receive concomitant medications in both cohorts until death. Health-state-specific resource use included outpatient visits, echocardiograms and community nurse visits; costs of CV-related hospitalisations and end of life care were applied based on the incidence (derived from ATTR-ACT) of patients requiring these resources per cycle. A scenario was also presented where the company explored the potential cost savings impact of the introduction of

tafamidis on reducing delays to diagnosis. This scenario required a number of assumptions, including the attribution of 100% of any reductions in time to diagnosis to tafamidis.

Disaggregated results highlight that the total acquisition cost of tafamidis is the key driver of incremental costs (meaning the model is highly sensitive to estimates of both the dose and average treatment duration). There is a small cost-offset due to reduced healthcare utilisation and CV-related hospitalisations. The main driver of QALY gains is due to the significant difference in projected survival for tafamidis, alongside a greater proportion of patients entering the earlier NYHA class II health state.

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. In addition, the submitting company indicated the list price results, change in life years and change in QALYs were also commercial in confidence. As a consequence, no health economic results can be presented.

A number of key sensitivity analysis scenarios were provided from the submitting company. The key sensitivities included the approach to extrapolation of survival and treatment discontinuation, the use of treatment-specific rather than pooled health state utility estimates, the use of age-adjustment of utilities and the removal of the stopping rule. Of particular interest are the combined scenarios, which are considered more plausible than the base case.

Key weaknesses:

- The Committee noted the lack of subgroup analysis in the economic model to explore the impact on the cost-effectiveness separately for wild-type and hereditary disease patients. While it was acknowledged this analysis would likely introduce additional uncertainty through the use of data from post-hoc subgroup analyses, it would have been helpful to explore this given the potential for the outcomes and clinical management of these patients to differ.
- A stopping rule has been applied which assumes all tafamidis-treated patients will discontinue treatment at NYHA Class IV (as a surrogate of end-stage heart failure). This rule was not applied within the clinical study nor is it stipulated within the marketing authorisation. Given the severity of the condition, and the observation that some patients reaching the NYHA class IV state subsequently transitioned to earlier states, it is unclear whether discontinuation of tafamidis would be appropriate in patients progressing to NYHA class IV. It was also highlighted by clinical experts that this could be very hard to implement in clinical practice as the treatment is well tolerated and patients can fluctuate between health states in a short amount of time. A scenario analysis excluding the stopping rule resulted in an increase from the base case.
- The approach to survival extrapolation is highly uncertain, and the models selected in the company base case appear overly optimistic. The use of a log-normal distribution for tafamidis and a generalised gamma for BSC, does not appear justified based on the assessment of statistical goodness-of-fit and may rely too heavily on the heavily censored latter stages of the observed Kaplan-Meier data. Numerous alternative distributions

appear equally plausible and fall within the 95% confidence intervals of the observed data. Statistical advice received by the SMC stated that the approach relied upon many assumptions without accounting for the combined error in the modelling, and that numerous distributions could be equally plausible. The Weibull distribution was deemed to be equally well-fitting by NDC, while still enabling the independent extrapolation of survival for each treatment arm. This was felt to be a plausible alternative approach to the base case estimate and resulted in significantly higher ICERs.

- Similarly, the approach to estimating treatment duration is uncertain and is likely to underestimate the plausible treatment duration with tafamidis. In fact, the use of the exponential function (best fitting by Bayesian Information Criterion [BIC]) results in the shortest duration of all approaches tested, while the gompertz model (best fitting by Akaike Information Criterion and second-best by BIC) results in the longest duration. The use of the lognormal function (the second best-fitting and second-longest estimates) highlights a significant sensitivity to this approach. It is also worth noting that, in contrast to the estimation of overall survival, treatment duration has not been risk-adjusted by NYHA class. This may add an additional degree of bias.
- Following treatment discontinuation, the clinical benefit of tafamidis is assumed to continue across the time horizon. As a result, patients may continue to move into less severe health states during the extrapolation phase, and achieve the same degree of survival benefits, despite no longer accruing the costs of active treatment. This assumption seems highly implausible; it would be more appropriate for patients to wane towards best supportive care probabilities from the point of discontinuation. This alternative approach results in higher ICERs, due to a lower proportion of patients moving into earlier health states over time.
- The submitting company has adjusted the medicine acquisition costs on the relative dose intensity and assumed that the remaining are not lost to wastage. The submitting company was asked to provide scenario analysis with a relative dose intensity of 100% to reflect the potential for wastage, resulting in a moderate increase in the ICER.
- The use of a single extrapolation matrix derived from the total 30 month study observation period assumes no change in the effectiveness of tafamidis over time. In addition, a gradual plateauing in transitions between classes was observed in the latter stages of the study period. The use of this ongoing treatment effect, derived based on the early study periods where more rapid improvements in NYHA class were observed, is likely to overestimate the effectiveness of tafamidis. A scenario using transition matrices based on observed data at month 18, 24 and 30 was deemed more appropriate.
- Utilities were not adjusted for increasing age and may therefore bias the result of the economic model in favour of tafamidis. A revised scenario was provided which applied age-adjustment in the extrapolation period, resulting in a moderate increase in the ICER. The provided analysis is believed to be an underestimate of the full effect of age-adjusted utilities, as the estimates used by the company for NYHA class I and II result in higher utilities than a healthy matched population.

- The assumption of a differential treatment effect on utilities, as well as assuming that patients will benefit from movement to earlier NYHA classes, creates the possibility of double counting the utility benefits of tafamidis. In addition, the treatment specific utilities do not reflect utility for patients who have discontinued tafamidis. The use of treatment-independent calculation of health effects would seem preferable to avoid this potential issue and result in an increased ICER.
- A number of alternative approaches described above were considered by NDC to be more methodologically appropriate and equally valid to the company's preferred approach. When combined, these resulted in a significant increase in the ICER. The ICER increased further still when the stopping rule was removed.

The Committee also 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 was unable to accept tafamidis for use in NHSScotland.

Additional information: guidelines and protocols

No published guidelines for the treatment of patients with wild-type or hereditary ATTR-CM were identified. The National Amyloidosis Centre in London provides a diagnostic, staging, monitoring and management advisory service for patients with amyloidosis in the UK.

The Heart Failure Association of the European Society of Cardiology published an expert consensus meeting report on a clinical practice update on heart failure in 2019. This includes the consensus recommendation that older patients with symptomatic heart failure, particularly those with heart failure with preserved ejection fraction (who are not hypertensive) or those who have features of hypertrophic or restrictive cardiomyopathy, or degenerative aortic stenosis and end-diastolic interventricular septal wall thickness exceeding 12 mm, should be considered for screening for cardiac ATTR. Tafamidis should be considered in patients with symptomatic heart failure due to confirmed ATTR (both autosomal dominant inherited disease and wild-type) in order to improve exercise capacity and quality of life, and to reduce cardiovascular hospitalisations and mortality. This recommendation is limited to patients who fulfil the inclusion and exclusion criteria of the ATTR-ACT study which includes confirmation of the presence of amyloid deposits on analysis of biopsy specimens obtained from the heart or other tissues (fat aspirate, gastrointestinal mucosa sites, salivary glands, or bone marrow).[10]

Additional information: comparators

No other medicines are licensed for the treatment of ATTR-CM.

Additional information: list price of medicine under review

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

Costs from BNF online on 3 March 2021. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 83 patients eligible for treatment with tafamidis in year 1 and 93 patients in year 5. The estimated uptake rate was 100% in year 1 and 100% in year 5 to which a confidential discontinuation rate was applied. This resulted in 66 patients estimated to receive treatment in year 1 rising to 75 in year 5.

These estimates make use of the average treatment duration estimated within the company's economic model, and as a result the treatment duration and overall cost may be underestimated.

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

References

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This assessment is based on data submitted by the applicant company up to and including 07 September 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.