NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy (review of TA696)

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tafamidis in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: February 2024

Note that this document is not NICE's final guidance on tafamidis. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tafamidis in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 19 March 2024
- Second evaluation committee meeting: 3 April 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Tafamidis is not recommended, within its marketing authorisation, for treating wild-type or hereditary transthyretin amyloidosis with cardiomyopathy (ATTR-CM) in adults.

1.2 This recommendation is not intended to affect treatment with tafamidis that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

ATTR-CM is a progressive condition that can lead to heart failure. Current treatment options are limited to managing symptoms and best supportive care. Tafamidis is the first treatment for ATTR-CM that aims to treat the condition.

Evidence from the main clinical trial shows that tafamidis reduces deaths and hospitalisations from conditions affecting the heart and blood vessels compared with placebo. There is longer-term follow-up evidence from this trial on how long people live when taking tafamidis and how long they take tafamidis for.

There are uncertainties in the economic model for tafamidis, including how long the effect of treatment lasts after it is stopped. The most likely cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources. So, tafamidis is not recommended.

2 Information about tafamidis

Marketing authorisation indication

2.1 Tafamidis (Vyndaquel, Pfizer) is indicated for ‘the treatment of wild-type or hereditary transthyretin amyloidosis in adults with cardiomyopathy (ATTR-CM)’.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tafamidis.

Price

2.3 The list price is £10,685.00 for 30 capsules of 61 mg tafamidis (excluding VAT; BNF online, accessed January 2024).

2.4 The company has a commercial arrangement, which would have applied if tafamidis had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by Pfizer, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Transthyretin amyloidosis (ATTR) is caused by abnormal transthyretin proteins being produced by the liver and accumulating as deposits in tissues of the body (amyloidosis). Transthyretin amyloidosis with cardiomyopathy (ATTR-CM) is a type of ATTR where most deposits accumulate in the heart. There are 2 types of ATTR-CM:

- Wild-type ATTR-CM, which is more common. It mostly affects older people and is more common in men.
- Hereditary ATTR-CM (also known as familial amyloid cardiomyopathy), which affects people born with inherited mutations in the transthyretin (TTR) gene.

The clinical experts explained that ATTR-CM is a progressive, life limiting and debilitating condition. For wild-type ATTR-CM, symptoms usually start in people aged 70 and over and for hereditary ATTR-CM, symptoms

usually start in people aged 60 and over. It can cause shortness of breath, palpitations and abnormal heart rhythms such as atrial fibrillation or atrial flutter, ankle swelling, fatigue, fainting and chest pain. The clinical experts noted that death in most people with ATTR-CM is from sudden death and progressive heart failure.

Burden of disease

3.2 As ATTR-CM progresses it can lead to the loss of mobility and independence, which affects quality of life for people with ATTR-CM and their carers as people become increasingly reliant on carers to do daily activities. In turn, carers may experience fatigue and isolation as they devote more time to caring. The patient expert explained that ATTR-CM significantly affects physical ability, noting that walking even short distances can be challenging. There is an associated financial burden as people, or their carers, may have to retire earlier than expected or travel long distances to specialist treatment centres. Delays in diagnosis can also cause anxiety for people living with symptoms without fully understanding what they are experiencing. In hereditary ATTR-CM, multiple family members can be affected, which can carry considerable psychological burden, such as anxiety and guilt about passing the condition on to children. The committee concluded that ATTR-CM is a debilitating condition that substantially affects both physical and psychological wellbeing.

Clinical management

Diagnosis

3.3 The clinical experts noted that the diagnosis pathway has changed since the ATTR-ACT trial was done. They explained that most people are now diagnosed using medical imaging, rather than biopsy, and more people are being diagnosed at earlier stages. But the clinical experts noted that many people with ATTR-CM are still not diagnosed. The patient expert also highlighted that even with the improvements seen in diagnosis,

without any disease-modifying treatments, early diagnosis is of limited value to people living with ATTR-CM. The committee noted that while the rate of diagnosis of ATTR-CM has increased rapidly, the condition is still likely to be underdiagnosed.

Comparators

3.4 The company considered that the most appropriate comparator for tafamidis in this indication is best supportive care (BSC). This is limited to the management of symptoms as well as supportive care, such as diuretics. A small number of people with ATTR-CM also have polyneuropathy with mixed clinical features. NICE's final scope included treatments for people with mixed phenotype ATTR as comparators. NICE has recommended 3 treatments for polyneuropathy:

- NICE technology appraisal guidance on vutrisiran for treating hereditary transthyretin amyloidosis
- NICE highly specialised technologies guidance on inotersen for treating hereditary transthyretin amyloidosis
- NICE highly specialised technologies guidance patisiran for treating hereditary transthyretin amyloidosis.

The company did not include these treatments as comparators in its submission because they had not been evaluated or licensed for people with ATTR-CM. The committee noted that the marketing authorisation for tafamidis did not specifically mention people with polyneuropathy. It acknowledged that, because it is rare for people to have both ATTR-CM and polyneuropathy, there would not be enough evidence to consider it separately. So, the committee agreed that vutrisiran, inotersen and patisiran could not be considered appropriate comparators. The final scope also included diflunisal as part of established clinical management without tafamidis. But the company had excluded diflunisal as a comparator because it is not licensed for ATTR-CM and there is no randomised controlled trial evidence for its use. Clinical experts stated

that people who have recently been diagnosed with ATTR-CM no longer have diflunisal because it is not well tolerated. The NHS England submission also stated people only have diflunisal for end-stage disease, and tafamidis is used at earlier disease stages. The committee agreed that diflunisal was not an appropriate comparator. The clinical experts noted that sodium-glucose co-transporter-2 (SGLT2) inhibitors have shown benefits in quality of life and survival in observational studies in people with ATTR-CM, but they are not part of established NHS practice in England. So, the committee agreed that SGLT2 inhibitors are not an appropriate comparator for tafamidis. The committee concluded that BSC was the only appropriate comparator.

Clinical effectiveness

Clinical effectiveness evidence

3.5 In the original NICE technology appraisal guidance on tafamidis for treating transthyretin amyloidosis with cardiomyopathy (from here referred to as TA696), the company gave evidence from 2 trials:

- ATTR-ACT (pivotal): a 30-month, phase 3 double-blind randomised controlled trial. It evaluated how effective, safe, and tolerable tafamidis was compared with placebo in adults with wild-type or hereditary ATTR-CM, who had a staging of 1 to 3 (n=441) based on the classification system from the New York Heart Association (NYHA).
- ATTR-ACT extension study (ATTR-ACT LTE): an open-label extension of ATTR-ACT including people from ATTR-ACT as well as people with ATTR-CM who did not take part in ATTR-ACT (ongoing; number of patients not reported).

The ATTR-ACT pivotal trial randomised people to have either 80 mg of tafamidis meglumine (n=176), 20 mg of tafamidis meglumine (n=88) or placebo (n=177) using a ratio of 2:1:2. Everyone who had treatment in the ATTR-ACT extension had tafamidis 61 mg, or tafamidis meglumine 80 mg if 61 mg was not available. The committee noted that the dose of

tafamidis used in ATTR-ACT was different to the dose in the marketing authorisation, which is 61 mg. But the marketing authorisation states that the relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at a steady state. For this evaluation, the company gave longer-term data collected from ATTR-ACT LTE with 84 months follow up (see section 3.6). The company did not present any new comparative evidence, for example tafamidis compared with any form of standard care. The EAG noted that the company had not updated the systematic literature review for clinical effectiveness data from TA696. The company explained that the ATTR-ACT trial and extension was the most robust data available for tafamidis. It noted that there is no real-world evidence available for tafamidis in England because it is not yet available. One of the clinical experts noted that newer real-world evidence is available from observational studies in other countries (France, Japan and the US) and that this supports the results of the ATTR-ACT trial and extension. The committee concluded that it would have preferred to see an updated systematic literature review for clinical effectiveness data. But it noted the comments from clinical experts that newer observational data supported the results of the ATTR-ACT trial and extension. So, the committee concluded that the clinical evidence given in this evaluation was suitable for decision making.

Longer-term data from ATTR-ACT LTE

3.6 The company gave new clinical effectiveness and safety evidence data from the August 2021 data cut of the ATTR-ACT LTE with 84 months of follow up. The company gave updated overall survival (OS) and time-to-treatment discontinuation (TTD) data for tafamidis only, which was censored for heart transplant, cardiac mechanical assist device (CMAD) implantation and loss to follow up. The exact figures are considered commercial in confidence by the company and cannot be given here. The company also provided all-cause mortality data for people in NYHA class 1 and 2 compared with people in NYHA class 3, and adverse events from the longer-term follow up. The committee noted that the other trial

outcomes that were specified in the scope, including cardiovascular-related mortality and hospitalisations, had not been included in the company submission. It noted that the ClinicalTrials.gov record for the ATTR-ACT LTE stated that cardiovascular-related mortality and hospitalisations were assessed at month 60. The company stated that only OS and TTD were available at 84 months and other outcomes had not been collected at every interval of the long-term extension study. The committee concluded that it would have liked to see all new data that was available since TA696 on the outcome measures specified in the scope.

Economic model

Company's modelling approach

3.7 Similarly to TA696, the company modelled the costs and benefits for tafamidis using a cohort-level Markov state-transition model. To capture the natural disease progression of ATTR-CM, model health states were based on the NYHA classification system. The model included 5 health states, 4 defined by NYHA classes (1, 2, 3, and 4) and death. People could move to a more severe health state (decline) or to a less severe one (improve). The company did not do an updated systematic literature reviews for economic evaluations, costs and resource use or utilities. The committee noted that the company used the same model structure as TA696 and considered that the company's model was suitable for decision making. It concluded that it would have preferred for the company to update its systematic literature reviews for economic evaluations, costs and resource use or utilities.

OS extrapolation

3.8 In TA696, the committee preferred the log-normal model to extrapolate OS for tafamidis. For this evaluation, the company used the longer-term data from ATTR-ACT LTE to fit parametric survival extrapolations for OS for tafamidis. The company's preferred OS extrapolation for tafamidis was the generalised gamma model. The company explained that the non-

parametric hazard profiles from ATTR-ACT LTE showed a clear peak at around 2 years, followed by a decline. It noted that only the log-logistic, log-normal and generalised gamma models are able to predict a local peak hazard as seen in the trial and that the generalised gamma model had the closest agreement with the non-parametric hazard estimators. The generalised gamma model also showed high goodness of fit to the observed data from ATTR-ACT LTE, because it had the lowest Akaike information criterion (AIC) value of all the candidate parametric survival models. The EAG highlighted that although the AIC value was low, the generalised gamma model had a higher Bayesian information criterion (BIC) value than the log-normal model, which suggests a worse fit to the observed data. The generalised gamma model also predicted the highest long-term survival estimates for tafamidis of all the candidate parametric survival models. The committee noted that the OS rate at 20 years for people having tafamidis predicted by the company's preferred generalised gamma model was relatively high, given that the average cohort age would be around 95 years at this time point. The exact survival rate is considered commercial in confidence by the company so cannot be reported here. The committee questioned the clinical plausibility of using the generalised gamma model. The company confirmed that survival estimates were capped to general population life tables. The committee noted that the choice of extrapolation model for OS did not have a large effect on the cost-effectiveness results. It concluded that it preferred to use the log-normal model to extrapolate OS for tafamidis, because it appeared to fit the observed data better and had more plausible long-term survival estimates than the generalised gamma model.

Treatment effect after stopping treatment

3.9 The EAG noted that, after the observed trial period, the company assumed that an increasing number of surviving people stopped having tafamidis but continued to have sustained treatment benefit without gaining any further treatment costs. It considered that this assumption

was unlikely to be clinically plausible. The EAG base case included the same assumption but also gave 2 scenarios:

- No further stopping of tafamidis after the observed trial period with continued treatment benefit and costs.
- People continuing to stop tafamidis after the observed trial period, with costs applied only to people still having tafamidis. Transition probabilities, adverse event rates, cardiovascular-related hospitalisations, survival and utilities for the BSC group were applied to people who stopped tafamidis, from the point that they stopped.

The clinical experts explained that once treatment with tafamidis is stopped, the TTR protein in the blood would revert to its normal behaviour and begin to form amyloid deposits. So, they considered that it is not plausible that there would be continued treatment effect after stopping tafamidis. They explained that in people who stopped treatment it was not known whether:

- amyloid formation would happen at the same rate as people who had not had tafamidis, but from a lower starting level of amyloid deposition, or
- there would be a 'catch-up effect' observed, so amyloid formation would happen at a higher rate than in people who had not had tafamidis.

The clinical experts also noted that they would not expect an immediate return to BSC outcomes in people who stopped treatment. The company highlighted that the observed 84-month data from ATTR-ACT LTE given in the company submission included both people who had tafamidis and those who had stopped treatment. So, it stated that its base case did not assume an indefinite treatment effect after tafamidis was stopped. The company highlighted a figure that it believed to show that the EAG's second scenario substantially underpredicts the observed OS and TTD from the ATTR-ACT LTE. The committee noted that the OS and TTD data

given by the company was censored for heart transplant, CMAD implantation and loss of follow up. The clinical experts noted that tafamidis would be stopped after having a heart transplant but would be continued on CMAD implantation. The committee noted that in TA696, it concluded that assuming continued treatment benefits after stopping tafamidis without a cost was overly optimistic and the EAG's analyses were suitable for consideration. The clinical experts stated that they would expect stopping treatment to continue after the observed trial period, so the committee concluded that the EAG's first scenario was not appropriate for decision making. The committee considered that given the mechanism of action of tafamidis, it was implausible that there would be a sustained treatment effect after stopping treatment. So, it considered that the company's base case, which assumed a sustained treatment effect without sustained treatment costs, was overly optimistic. The committee heard from the clinical experts that outcomes would not immediately revert to BSC outcomes when treatment is stopped, so the EAG's second scenario was likely conservative. So, the committee considered that none of the scenarios available accurately reflected what was likely to happen in clinical practice. Given the uncertainty, the committee concluded that the second EAG scenario, which assumed BSC outcomes when stopping treatment, was the most appropriate for decision making. The committee acknowledged that the second EAG scenario was likely conservative, so considered that this would be reflected in the preferred cost-effectiveness range (see section 3.12). The committee also considered that it would have been helpful to see how modelled treatment effect changes over time given in a graph of implied hazard ratios.

Utility values compared with UK age-matched average

3.10 In the company submission the utility values for people in the NYHA class 1 (in both tafamidis and BSC arms) and class 2 (tafamidis arm) were higher than the UK general population age-matched average. The exact utility values are considered commercial in confidence by the company and cannot be given here. The company considered that people in NHYA

class 1 typically do not have symptoms and physical activity limitations and people in NYHA class 2 only experience slight difficulties with physical activity. But the general population of the same age may have other conditions that affect their quality of life. The committee noted that the starting age in the economic model was 74 years. The EAG base case included capped utility values to the age-matched equivalent. The clinical experts explained that it was not plausible that someone with ATTR-CM would have a better quality of life than someone of a similar age from the general population. So the committee concluded that capped utility values for the NYHA class 1 and NYHA class 2 health states were appropriate for decision making.

Treatment dependency of utility values

3.11 In TA696, the committee concluded that BSC values (treatment-independent) and utility values should be applied for the NYHA class 4 health state because:

- there was a substantial difference in utility values between arms in NYHA class 4, while utility values for tafamidis and BSC in the other NYHA classes were similar and
- NYHA class 4 utility values were based on a low number of observations.

The company stated in its submission and in the committee meeting that it had applied treatment-independent utility values in the NYHA class 4 health state. But in its response to clarification questions from the external assessment group, it stated that people having tafamidis in the NYHA class 4 health state would have the utility value for tafamidis from ATTR-ACT and would only be assigned the utility value for BSC after stopping treatment. The EAG preferred to use the same utility values for the tafamidis and BSC arms for NYHA class 4, for people having treatment as well as those who stopped. The committee considered the treatment-dependent utility values applied for NYHA health states 1 to 3 and noted

that for some health states the tafamidis value was higher, but in other health states the BSC value was higher. The committee asked what the clinical justification was for this and whether scenarios had been done applying treatment-dependent utility values for all health states. The company said it did not have scenarios exploring this. The committee heard the concerns raised about the reliability of the treatment-dependent values for NYHA class 4 and concluded that using BSC utilities was more appropriate for decision making. The committee would have also preferred to see a decision for using treatment-dependent utility values for NYHA health states 1 to 3 and scenarios exploring treatment-dependent utility values for all health states.

Cost-effectiveness estimates

Acceptable incremental cost-effectiveness ratio (ICER)

3.12 NICE's manual on health technology evaluation notes that above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, decisions about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the evidence presented, but will also take into account other aspects including uncaptured health benefits. The committee noted that:

- there are currently no disease-modifying treatments available for people with ATTR-CM in England, so there is substantial unmet need in this population (see section 3.4)
- the company had given 84-month follow-up data for people having tafamidis, but no new comparative data was available since TA696 (see section 3.6)
- there is uncertainty about the outcomes in people who stopped treatment with tafamidis, but that the committee's preferred assumptions are likely to be conservative (see section 3.9).

So, based on the evidence available at the first committee meeting and the resulting committee conclusions, the committee agreed that an acceptable ICER would be towards the upper end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Cost-effectiveness estimates

3.13 The company cost-effectiveness estimates are considered to be commercial in confidence by the company so cannot be reported here. The company's preferred analysis estimated that the deterministic and probabilistic ICERs for tafamidis compared with BSC were at or above the upper end of the range normally considered a cost-effective use of NHS resources (including the company's confidential commercial arrangement). It included the following assumptions:

- using a generalised gamma parametric distribution function to model OS for tafamidis (see section 3.8)
- using treatment-dependent utility values for the NYHA class 4 health state (see section 3.10).

The committee agreed that the company's analysis did not include all of its preferred assumptions. It noted that the EAG's preferred analysis was different from the company's preferred analysis and more in line with the committee's preferred assumptions. Specifically, the committee agreed with the following changes in the EAG's analysis:

- using a log-normal parametric distribution to model OS for tafamidis (see section 3.8)
- applying a cap on health state utility values above the general population age-matched average for NYHA class 1 and 2 for tafamidis and BSC (see section 3.10)
- using BSC outcomes for NYHA class 4 instead of treatment-dependent utility values (see section 3.11).

These changes resulted in an ICER that was above the upper end of the range normally considered a cost-effective use of NHS resources. Also, the committee preferred to apply the EAG's second exploratory scenario for modelling treatment effect for people who stopped having tafamidis. Using the assumptions in the EAG's scenario further increased the ICER above the range that NICE usually considers an acceptable use of NHS resources. The committee would also have liked to have seen:

- updated data from ATTR-ACT LTE on all outcomes measures specified in the final scope, where available, such as cardiovascular-related mortality and hospitalisations at week 60 (see section 3.6)
- how the modelled treatment effect changes over time given in a graph of implied hazard ratios (see section 3.9)
- a scenario where treatment-independent utility values were used for all health states (see section 3.11).

So, it concluded that tafamidis was not a cost-effective use of NHS resources for treating ATTR-CM.

Other factors

Equality

3.14 The committee noted comments from the clinical and patient experts that the hereditary form of ATTR-CM disproportionally affects people with certain variants (such as Val122Ile), which are more prevalent in people of African Caribbean and Hispanic ethnicities. In these populations, ATTR-CM is often diagnosed later and has worse outcomes than in other people with ATTR-CM. Val122Ile is not associated with polyneuropathy so people with this variant do not have access to disease-modifying therapy. The professional group submissions also highlighted the fact that prescribing tafamidis might be restricted to specialist centres and that people with ATTR-CM are often older and could experience difficulties with travelling long distances to have treatment. The committee took these factors into

account in its decision making but agreed that this was not something that could be addressed in its recommendation.

Conclusion

Tafamidis is not recommended

3.15 The committee noted that there are no disease-modifying treatments for ATTR-CM available in England and acknowledged the substantial unmet need in this population. It also noted that there is uncertainty about the outcomes in people who have stopped treatment with tafamidis, but that the committee's preferred assumptions are likely to be conservative. So, an acceptable ICER based on this set of assumptions would be towards the upper end of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). The cost-effectiveness estimates that included the committee's preferred assumptions were above the upper end of range that NICE usually considers an acceptable use of NHS resources. So, tafamidis is not recommended.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Emma Bajela

Technical lead

Lizzie Walker

Technical adviser

Kate Moore

Project manager

ISBN: [to be added at publication]