

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy

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 appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

The appraisal 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 race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

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

After consultation:

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

For further details, see [NICE's guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 24 June 2020

Second appraisal committee meeting: To be confirmed

Details of membership of the appraisal committee are given in section 5.

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 can lead to heart failure, but treatment options are limited to managing symptoms and best supportive care. Accurately diagnosing ATTR-CM is challenging and can take a long time.

Tafamidis is the first treatment for ATTR-CM that aims to treat the disease. Evidence from clinical trials shows that it reduces deaths and hospitalisation from conditions affecting the heart and blood vessels compared with placebo. But inconsistent results on how effective tafamidis is for different types and stages of ATTR-CM mean that the evidence is uncertain. Also, the measure used to assess how severe ATTR-CM is has limitations, so it is difficult to identify who benefits from treatment and decide who should stop.

Because of this, and uncertainty about the assumptions related to early diagnosis and how long the treatment works after it is stopped, the cost-effectiveness estimates are very uncertain. They 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 (Vyndaqel, Pfizer) is indicated for ‘the treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM)’.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics](#).

Price

- 2.3 The price of tafamidis is £10,685.00 per 30-capsule pack of 61 mg capsules (excluding VAT; company submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee ([section 5](#)) considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), the technical report, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- In the economic model, people whose disease is classed as New York Heart Association (NYHA) 1 to 3 should be assumed to remain on treatment (issue 2, see technical report pages 14 to 15).
- Utility values for best supportive care should be applied to everyone in the NYHA 4 model health state (issue 3, see technical report pages 15 to 18).

- In the model it is acceptable that an age adjustment is applied to health state utility values after the observed trial period (issue 3, see technical report pages 15 to 18).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, pages 22 to 23), and took these into account in its decision making. It discussed the following issues (issues 1, 2, 4 and 5), which were outstanding after the technical engagement stage.

The condition

ATTR-CM can lead to heart failure and sudden death

3.1 The committee understood that there are 2 causes of transthyretin amyloidosis with cardiomyopathy (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 TTR gene.

The clinical experts explained that ATTR-CM is a progressive disease. Symptoms usually start after the age of 70 in people with wild-type ATTR-CM or after the age of 60 in people with hereditary ATTR-CM. 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. They noted that death in most people with ATTR-CM is from sudden death and progressive heart failure. The committee concluded that ATTR-CM can lead to heart failure and sudden death.

ATTR-CM significantly affects mental and physical wellbeing

3.2 The patient experts explained that ATTR-CM significantly affected their physical ability. For example, one noted that walking even short distances could be challenging, while another stated that they were no longer able to do their daily physical activities. They noted that ATTR-CM also

affected psychological wellbeing, for example, symptoms of breathlessness leading to anxiety. Loss of independence and an increased reliance on caregivers was also highlighted as a cause of depression related to the condition. The patient experts explained that psychological effects can be exacerbated for people with hereditary ATTR-CM because it can affect multiple members of a family, and there was anxiety about passing it on to children. The committee concluded that ATTR-CM is a debilitating disease which significantly affects mental and physical wellbeing.

Clinical management

Accurately diagnosing ATTR-CM is challenging and can take a long time

3.3 The patient experts explained that getting an accurate diagnosis for ATTR-CM could be challenging. Awareness of the condition, and the type of ATTR-CM a person has (see section 3.1), can vary and lead to delays to diagnosis. The company estimated that it took 3 years or more for a person to be accurately diagnosed with ATTR-CM. The clinical experts agreed that there were challenges in diagnosing ATTR-CM accurately, but noted that there had been developments in recent years. Radionuclide imaging (DPD scans), a test usually used to detect bone abnormalities, is very sensitive to detecting amyloid deposits in the heart and is being increasingly used to diagnose ATTR-CM. But, they noted that transthyretin amyloid deposits are often an incidental finding in people having DPD scans. They explained that the population they see in practice had a range of amyloid deposits, sometimes because of older age, for example. Also, there is no defined point at which amyloid deposits become amyloidosis. So, it is unclear why some amyloid deposits progress to amyloidosis and others do not. Also, because other common comorbidities can lead to increased breathlessness and decreased mobility, a definitive ATTR-CM diagnosis is challenging. The clinical experts and the NHS England representative explained that when amyloidosis is suspected people are referred to the National Amyloidosis

Centre for more rigorous testing. The committee concluded that accurately diagnosing ATTR-CM is challenging, and can take a long time.

Best supportive care is the relevant comparator

3.4 Treatment options for ATTR-CM are limited to managing symptoms and supportive care, such as diuretics. A small proportion of people with ATTR-CM also have polyneuropathy (a mixed phenotype). NICE has recommended 2 treatments for polyneuropathy:

- [NICE highly specialised technologies guidance on inotersen for treating hereditary transthyretin amyloidosis](#)
- [NICE highly specialised technologies guidance on patisiran for treating hereditary transthyretin amyloidosis](#).

NICE's final scope included inotersen and patisiran as comparators to tafamidis. The committee noted that the company had not included these treatments as comparators in its submission because neither had been evaluated in people with ATTR-CM. The committee noted that the marketing authorisation for tafamidis 61 mg did not specifically mention people with polyneuropathy. It acknowledged that because it is rare for people to have ATTR-CM and polyneuropathy, there would not be enough evidence to consider it separately. So, it agreed that inotersen and patisiran could not be considered as comparators to tafamidis. The committee also noted that liver or heart transplantation are options for some people with ATTR-CM and a specific genetic mutation. But it recognised that because this mutation is uncommon in England, and that transplantation can only take place early in the course of the disease, transplants are rarely done. The committee agreed that transplantations were not an appropriate comparator for tafamidis and concluded that best supportive care was the appropriate comparator.

Measuring the severity of ATTR-CM using the NYHA classification system has limitations

3.5 The NYHA functional classification system is commonly used in clinical practice to assess heart failure, and is sometimes used to measure the severity of ATTR-CM. It groups symptoms into 1 of 4 classes depending on how limited a person's physical activity is. A person whose disease was classed as NYHA 1 would be able to do ordinary physical activity and someone whose disease was classed as NYHA 4 would be unable to do physical activity without feeling discomfort. The clinical experts explained that although NYHA classification is used in clinical practice, it has limitations. Because it is a patient-reported measure it can vary from day to day, and there can be inconsistencies in people's symptoms. For example, people with the same activity tolerance may classify their level of heart failure differently. The clinical experts commented that it was also difficult to identify whether movement between the NYHA classes was a result of ATTR-CM progressing or changes in other comorbidities. One of the clinical experts suggested that a measure based on cardiac markers such as B-type natriuretic peptide and glomerular filtration rate had potential to identify disease stage and who is benefiting from treatment, but evidence of its use in ATTR-CM in clinical practice was limited. The committee concluded that using NYHA classification in ATTR-CM had limitations.

It is not appropriate to define starting and stopping rules for tafamidis based only on the NYHA classification system

3.6 The committee noted that the marketing authorisation for tafamidis did not specify starting and stopping rules for tafamidis based only on the NYHA classification system. It noted that the marketing authorisation states 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 3, 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'. The company submission included analyses with these starting and stopping rules:

- people whose disease is classed as NYHA 1 or 2 can start tafamidis
- people whose disease is classed as NYHA 1, 2 or 3 can keep taking tafamidis and
- people should stop tafamidis if their disease progresses to NYHA 4.

The ERG explained that it had concerns about the clinical relevance of only allowing people whose disease is classed as NYHA 1 or 2 to start treatment. The committee recalled that NYHA 1 means that people can do ordinary physical activity (see section 3.5). It considered if tafamidis would be used for people who are easily able to do the activities of daily living (no functional limitations). The clinical experts explained that they would have reservations about offering treatment to people whose disease is classed as NYHA 1 because they have no functional limitations and might not benefit from treatment. The company's proposed stopping rule for NYHA 4 was not in the marketing authorisation for tafamidis. The ERG questioned if it would work in practice because the lack of alternative treatments meant people would likely prefer to keep taking tafamidis. The clinical experts explained that people's disease often varies between NYHA 3 and 4 and that this was typical of ATTR-CM. They also noted that some people whose disease was classed as NYHA 4 could improve, so could change to NYHA 3 or lower. The ERG noted that improvements shown by changes in NYHA class were also seen in ATTR-ACT. The committee considered that the NYHA classification could not be used to accurately identify people who need treatment. So, it concluded that defining starting and stopping rules for tafamidis based only on the NYHA classification system was not appropriate.

It is unclear if introducing tafamidis would reduce delays in diagnosis times

3.7 At technical engagement, the company highlighted that introducing tafamidis reduced delays to ATTR-CM diagnoses. It noted that the availability of tafamidis would result in ATTR-CM being detected earlier because of more awareness among cardiologists. It also noted that a trend of earlier diagnosis had been seen when tafamidis was available through the Early Access to Medicines Scheme (EAMS). A statement from NHS England partly supported the company's view and highlighted that ATTR-CM is often misdiagnosed. It suggested that if NICE recommended tafamidis, and awareness was increased through educational campaigns, diagnosis rates may improve. The ERG highlighted that the trend of earlier diagnosis seen during the EAMS period could be explained by improvements in diagnostic tools since the ATTR-ACT trial (see section 3.3). Also, it noted that awareness of ATTR-CM had increased after patisiran and inotersen were introduced (see section 3.4). So, diagnosis times are unlikely to substantially change if tafamidis was to be recommended by NICE. The committee also noted that data from the National Amyloidosis Centre suggested that a third of people had an accurate ATTR-CM diagnosis within 6 months. It acknowledged this was an improvement on current diagnosis delays, but recognised these diagnoses were made at a specialist centre and questioned if this could be done in clinical practice. The committee concluded that it was unclear to what extent, if any, introducing tafamidis would reduce ATTR-CM diagnosis delays.

Clinical evidence

The ATTR-ACT studies are appropriate for decision making

3.8 The clinical evidence came from 2 studies:

- 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, whose disease was classed as NYHA 1 to 3 (n=441).

- ATTR-ACT extension study: an open-label extension of ATTR-ACT including patients from ATTR-ACT and others with ATTR-CM who did not take part in ATTR-ACT (ongoing; number of patients not reported).

The ATTR-ACT study randomised patients to have 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 for tafamidis, which is 61 mg. But, the marketing authorisation stated that the relative bioavailability of tafamidis 61 mg is similar to tafamidis meglumine 80 mg at a steady state. So, the committee concluded that the ATTR-ACT studies were appropriate for decision making.

Tafamidis is more effective than placebo in clinical trial results

- 3.9 The primary analysis from ATTR-ACT compared the results of a pooled tafamidis (20 mg and 80 mg doses) treatment group with the placebo group. The primary outcome, a combined measure of mortality and cardiovascular-related hospitalisations, was assessed in a hierarchical analysis using the Finkelstein-Schoenfeld method. The primary outcome measured differences in all-cause mortality and the frequency of cardiovascular-related hospitalisations between tafamidis and placebo. Of those alive at month 30, people who had tafamidis had fewer annual cardiovascular-related hospitalisations (0.297) on average than those who had placebo (0.455) and differences were statistically significant. The committee considered that this measure was not used in clinical practice, so it was unclear what the relevance of these results was to people with ATTR-CM who would be seen in clinical practice. It also considered the secondary outcome results from ATTR-ACT and noted that at month 30

compared with placebo, tafamidis was associated with statistically significant reductions in:

- cardiovascular-related mortality
- cardiovascular-related hospitalisations
- mobility decline (assessed using the 6-minute walk test).

The committee concluded that tafamidis could be considered more effective than placebo based on the evidence presented.

The subgroup analyses raise concerns about the clinical effectiveness of tafamidis but are not robust

3.10 The committee considered the predefined subgroup analyses from ATTR-ACT, specifically those examining the effectiveness and safety of tafamidis in:

- hereditary and wild-type ATTR-CM (see section 3.1) and
- either NYHA 1 or 2 or NYHA 3 disease.

The analyses of hereditary and wild-type ATTR-CM found that the observed benefit of tafamidis compared with placebo for the primary outcome was driven by wild-type ATTR-CM (the results are considered confidential by the company and cannot be reported here). But when the parts of the primary outcome were analysed separately different results were seen. For cardiovascular-related mortality, the hazard ratios favoured tafamidis over placebo, but the differences were not statistically significant in either wild-type (hazard ratio 0.71 [95% confidence interval 0.47 to 1.05]) or hereditary ATTR-CM (hazard ratio 0.69 [95% confidence interval 0.41 to 1.17]). Forest plots included in the summary of product characteristics for tafamidis showed that there were statistically significant reductions in hospitalisations for people with wild-type ATTR-CM who had tafamidis. But, no statistically significant differences were seen in people with hereditary ATTR-CM (relative risk ratios are considered confidential by the company and cannot be reported here). The same forest plots

showed tafamidis statistically significantly improved cardiovascular-related mortality and the rate of cardiovascular hospitalisations if a person's disease was classed as NYHA 1 or 2, but not if it was classed as NYHA 3. The clinical experts suggested that the subgroup results could mean that a large proportion of people with ATTR-CM would not benefit from tafamidis. The company highlighted that the relatively small number of people included in the subgroup analyses from ATTR-ACT meant it was inappropriate to place too much weight on the statistical significance of the comparisons. The committee accepted the company's point about a lack of statistical power in the subgroup analyses. But, it agreed that the subgroup results added to the uncertainty about the effectiveness of tafamidis in people with hereditary ATTR-CM and in people with ATTR-CM classed as NYHA 3. The company also presented data from EAMS which suggested a trend towards earlier diagnosis and treatment in greater proportion of people with less severe disease (NYHA 1 or 2; see section 3.7). The committee acknowledged the trend, but noted that there was no evidence from EAMS that showed a different effect of tafamidis when it was started in the less severe NYHA classes. So, it agreed that it was unclear if there were any additional benefits to starting tafamidis when ATTR-CM is less severe and classed as NYHA 1 or 2. It concluded that the subgroup analyses raised concerns and uncertainty about the clinical effectiveness of tafamidis.

Quality of life

Tafamidis is more effective than placebo in slowing the decline in quality of life

3.11 Quality of life was measured in ATTR-ACT using 3 scales: the Kansas City Cardiomyopathy Questionnaire (KCCQ), EQ-5D-3L and EQ-5D visual analogue scale. The company explained that the KCCQ is a valid and reliable measure of health status for people with heart failure. It measures physical function, symptoms (frequency and severity), social function and quality-of-life domains, and calculates an overall summary score with lower scores showing worse impairment. The committee noted that the

KCCQ overall summary score results from ATTR-ACT showed that from baseline to month 30, people taking tafamidis had a slower decline in quality of life than people taking placebo (least squares mean difference compared with placebo 13.65 [p<0.0001]). The committee also noted the results measured by the EQ-5D-3L and EQ-5D visual analogue score (these are considered confidential by the company and cannot be reported here). The committee concluded that compared with placebo, tafamidis slowed the decline in quality of life for people with ATTR-CM.

Adverse events

Tafamidis is a safe and well-tolerated treatment

3.12 Most of the adverse events of treatment seen in ATTR-ACT were mild to moderate in severity, with fewer in the tafamidis treatment groups. The company highlighted that the proportion of people reporting serious events was higher in the placebo group. The committee concluded that tafamidis was generally safe and well tolerated.

The company's economic model

The company's economic model can be considered for decision making because no alternative to NYHA health states is available

3.13 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 (see section 3.5). The model included 5 health states, 4 defined by NYHA classes (1, 2, 3, and 4) and 5 being death. People can move to a more severe health state (decline) or to a less severe one (improve). The company explained that because NYHA classification captured aspects of functional limitation and symptom severity it was suitable to model changes in ATTR-CM. It also highlighted that NYHA classification predicted health-related quality of life and survival well, and it had been widely used in cost-effectiveness models.

The committee recalled its concerns about the NYHA classification system (see section 3.5), but concluded that because there was no available alternative the company's model could be considered for decision making.

Assumptions in the economic model

A stopping rule for tafamidis based on NYHA classification should not be included in the economic model

3.14 Both the company's and ERG's analyses after technical engagement included a stopping rule for tafamidis, which assumed that people would stop treatment if their disease progressed to NYHA 4. The committee noted the limitations of using the NYHA classification system in clinical practice and the lack of evidence about tafamidis' effectiveness beyond NYHA class 1 and 2 (see sections 3.5, 3.6 and 3.10). It also noted that the marketing authorisation for tafamidis stated that there were limited clinical data in patients whose disease was classed NYHA 4 but did not specify that it should be stopped. The committee concluded that although there were limited clinical data in patients whose disease was classed as NYHA 4, it was not appropriate to model a stopping rule based on the NYHA classification. This was because it was not specified in the marketing authorisation and would be challenging to do in clinical practice.

It is unrealistic to assume continued treatment benefits without a cost

3.15 After technical engagement, the company included a treatment stopping function for people in the NYHA 1 to 3 health states. During technical engagement, a clinical expert explained that it was unlikely people would stop tafamidis in NYHA 1, 2, or 3. This was because it was unclear when a person's disease changes from one NYHA class to another, and that people usually prefer to remain on treatment if there are no alternatives. Also, because tafamidis is well tolerated and easy to take, a high rate of adherence would be expected. After technical engagement, the company acknowledged this, but included a treatment stopping rule for people in

the NYHA 1 to 3 health states in its revised analysis. The ERG explained that in the economic model, people in the NYHA 1 to 3 health states who stop treatment with tafamidis are assumed to benefit from treatment indefinitely without any treatment costs. The clinical experts who responded to technical engagement suggested it was unreasonable to assume that treatment benefits would be maintained indefinitely after treatment stops. The committee concluded that assuming continued treatment benefits without a cost was overly optimistic and would lead to an underestimated incremental cost-effectiveness ratio (ICER).

The ERG's continued treatment benefit analyses are suitable for consideration

3.16 The ERG presented 2 alternative analyses that used different assumptions about continued treatment benefits in the NYHA 1 to 3 health states:

- The first analysis continued to model treatment stopping in NYHA 1 to 3 health states during the observed clinical trial period. But after the clinical trial period finished it assumed that all people having tafamidis would remain on treatment, and treatment benefits and costs would continue.
- The second analysis assumed that people having tafamidis in NYHA 1 to 3 health states would stop treatment at the same rate assumed in the company's analysis (see section 3.15), but after stopping tafamidis, costs and outcomes would revert to those of best supportive care. In the company's analysis people still benefited from tafamidis after stopping treatment.

In both analyses, when disease progressed to NYHA 4, everyone would stop tafamidis and have best supportive care. The committee recalled that it would not consider a stopping rule based on the NYHA classification (see section 3.14), but agreed it would consider the ERG's alternative continued treatment benefit analyses. It considered that some people would likely stop tafamidis for reasons other than disease progression or

death, for example adverse events or older age. So, it agreed it was implausible to assume that all people in the NYHA 1 to 3 health states would remain on treatment indefinitely after the clinical trial period. It also acknowledged that reverting to best supportive care outcomes after stopping treatment would be conservative. This was because the estimates of tafamidis' treatment effects already included people who stopped treatment during the trial period. But, the committee agreed that people stopping tafamidis would go on to have best supportive care and that these costs should be included in the model. On balance, the committee recognised that both of the ERG's alternative analyses had limitations, but agreed they provided realistic alternatives to the company's overly optimistic analyses. The committee concluded that the ERG's analyses were appropriate for decision making, but agreed that a stopping rule should not be included.

Overall survival beyond the observed trial period should be estimated using a log-normal extrapolation function

3.17 After technical engagement the company modelled overall survival beyond the observed trial period, using generalised gamma extrapolation functions for tafamidis and best supportive care. The ERG explained that the company had changed the extrapolation function it used from log-normal to generalised gamma, which had more favourable results for tafamidis. The ERG highlighted that although the company acknowledged that the extrapolations based on generalised gamma were optimistic, it had not given a reason for revising this aspect of its analysis at technical engagement (for example, statistical goodness-of-fit or external clinical validation). The company explained that it changed the extrapolation in its revised analysis to make use of a new data cut and more data from ATTR-ACT. The committee concluded that the reason for using generalised gamma functions to model overall survival was unclear and agreed to consider only the log-normal extrapolation functions in its decision making.

The company's early diagnosis assumptions are not appropriate for decision making

3.18 After technical engagement, the company provided analyses that used 3 new assumptions about early ATTR-CM diagnosis. It assumed that:

- introducing tafamidis reduced the average age of starting treatment by 2.5 years to 71.95 years
- £20,000 of avoidable health care costs would be incurred during the time people waited for a correct diagnosis
- diagnosis delays lead to avoidable anxiety and depression.

The company highlighted that some hospital, primary care and imaging resource use might be avoided through earlier diagnosis, but acknowledged it was not possible to be more definite. But it noted that the cost saving assumption showed that earlier diagnosis of ATTR-CM could affect cost-effectiveness estimates. It also derived an anxiety- and depression-related disutility value using EQ-5D-3L and highlighted that this disutility could be avoided if ATTR-CM diagnosis delays were reduced. It acknowledged that not all people would have depression but the analysis showed the potential effect of earlier diagnosis on people's quality of life. The ERG highlighted that it was unclear how the company had estimated that diagnosis delays could be reduced by 2.5 years and how potential cost savings of £20,000 had been estimated. It also considered that applying a quality-adjusted life year (QALY) gain for reduced anxiety or depression for all patients was not a reasonable approach because it was not supported by any evidence. The committee considered if being diagnosed with a serious cardiac condition could negatively affect a person's mental wellbeing and acknowledged it may change the way they view themselves, and how their families perceive them. The company explained that it had not investigated the effects of a diagnosis of ATTR-CM on psychological wellbeing. It recalled that it was unclear if introducing tafamidis would reduce delays in diagnosis (see section 3.7), and agreed that it was unlikely delays could be reduced by

2.5 years. The company also presented a subgroup analysis which assumed, because ATTR-CM was diagnosed earlier, everyone would start tafamidis when their disease was less severe and classed as either NYHA 1 or 2. The committee considered if the subgroup analyses were relevant to clinical practice, and noted that the proportion of people in each model health state did not reflect the EAMS data (see sections 3.7 and 3.10). It also noted that estimates of cost effectiveness were different for the subgroup compared with the full population. But, it recalled that it was unclear if there were any additional benefits to starting tafamidis when ATTR-CM is classed as NYHA 1 or 2 (see section 3.10). It agreed that the cost-effectiveness estimates for the subgroup were uncertain and agreed it would not consider them further. The committee agreed that the extent that reducing diagnostic delays could lead to cost savings or reduced quality-of-life losses was unclear. It concluded that the company's early diagnosis assumptions were not appropriate for decision making because there was not enough evidence to support them.

Including drug wastage costs is appropriate

3.19 After technical engagement, the ERG included potential tafamidis drug wastage in its estimate of costs. The committee considered if drug wastage would be substantial for tafamidis. The NHS England representative explained that they did not have any data on tafamidis wastage, so did not know whether it would be significant or not. The committee agreed with the principle of including drug wastage in its analysis and acknowledged that including it had little effect on the cost-effectiveness estimates. So, the committee concluded that it was appropriate to include drug wastage costs in its preferred analysis because some wastage was likely to happen in clinical practice.

Utility values

NYHA health state utility values are appropriate for decision making

3.20 The company derived health state utility values using EQ-5D-3L utility data from ATTR-ACT. The committee recalled that the company had also collected quality-of-life data using the KCCQ measure, which included function domains (see section 3.11). However, it agreed that the EQ-5D-3L data were more suitable for the economic model because they were in line with the reference case. The committee recalled its concerns about using health states based on NYHA classes in the model structure, but agreed that they could be considered because there was no available alternative (see section 3.13). The committee concluded that the company's health state utility values were appropriate for decision making.

Utility values should be adjusted for age after the observed trial period

3.21 Before technical engagement, the company's analysis did not adjust health state utility values to account for the effect of increasing age. The ERG highlighted that this meant utility values for tafamidis and best supportive care were better than for the age-equivalent general population. The clinical experts involved in technical engagement explained that it was not plausible that someone with ATTR-CM could have a better quality of life than someone of a similar age and sex from the general population. The company adjusted its utility values to take account of increasing age after the observed trial period in its revised analyses after technical engagement analyses. The committee concluded that using age-adjusted utility values was appropriate.

Best supportive care utility values should be applied in the NYHA 4 health state

3.22 The company estimated health state utility values separately for each NYHA class (see section 3.20) and treatment included in the model. The company explained that different health state utility values between

tafamidis and best supportive care may reflect differences in hospitalisations and adverse events associated with each treatment. The committee recalled that the NYHA classification system was unlikely to be sensitive to changes in ATTR-CM (see section 3.5). The ERG noted that the company modelled substantially different on-and off-treatment utility values in the NYHA 4 health state. It also explained that estimates of NYHA 4 utility values were based on very few observations. The company highlighted that the health state utility values were derived from EQ-5D-3L data from ATTR-ACT and were the most appropriate data for the economic analysis. The ERG noted that in ATTR-ACT quality-of-life data were collected only during the on-treatment period, and that in the trial, most people stopped treatment before their disease progressed to NYHA 4. The ERG explained that the estimated NYHA 4 utility value for tafamidis could be affected by informative censoring, because the quality of life of anyone who stopped tafamidis in NYHA 4 was not captured. To account for this, the ERG's analysis after technical engagement assumed that the estimated best supportive care utility value applied to everyone in the NYHA 4 health state. After technical engagement the company accepted that it was appropriate to apply best supportive care utility values in NYHA 4 and it used this assumption in its revised analysis. The committee agreed that it had concerns about using treatment-dependent health state utility values from relatively few observations and the potential for informative censoring to bias these estimates. It concluded that the treatment-dependent utility values were reasonable in NYHA 1 to 3, and that best supportive care utility values should be applied in the NYHA 4 health state.

Cost-effectiveness estimates

Because of the high levels of uncertainty an acceptable ICER is around £20,000 per QALY gained

3.23 [NICE's guide to the methods of technology appraisal](#) notes that above a most plausible ICER of £20,000 per QALY gained, judgements 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 ICERs presented.

The committee noted the high level of uncertainty, specifically:

- measuring the clinical effectiveness of tafamidis using the NYHA classification system (see section 3.5)
- the relevance of trial outcomes to people in clinical practice and the effectiveness of tafamidis in people with hereditary ATTR-CM and in people with ATTR-CM classed as NYHA 3 (see sections 3.9 and 3.10)
- starting and stopping rules based on the NYHA classification system (see sections 3.6 and 3.14)
- if treatment benefits continue after stopping tafamidis (see section 3.15)
- if introducing tafamidis would reduce diagnosis delays, and if there would be any cost savings or quality-of-life benefits because of this (see sections 3.7 and 3.18).

So, the committee agreed that an acceptable ICER would be around £20,000 per QALY gained.

Tafamidis is not a cost-effective use of NHS resources

3.24 The company's preferred analysis estimated that the ICER for tafamidis compared with best supportive care, in the full population, was less than £30,000 per QALY gained (including the company's confidential commercial arrangement). The committee understood that company's preferred analysis included the following assumptions:

- a stopping treatment function for tafamidis in NYHA health states 1, 2 and 3 (see section 3.15)
- using a generalised gamma extrapolation function to model overall survival (see section 3.17)

- a stopping treatment rule for tafamidis if disease progressed to NYHA 4 (see section 3.14)
- an earlier treatment starting age and estimated cost savings and benefits associated with earlier diagnosis of ATTR-CM (see sections 3.7 and 3.18)
- health state utility values adjusted for age (see section 3.21)
- treatment-independent health state utility values in NYHA 4 equal to best supportive care values (see section 3.22).

The committee agreed that the company's analysis did not include all of its preferred assumptions. It noted that the ERG'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 ERG's analysis:

- assuming people in NYHA health states 1, 2 and 3 keep taking tafamidis and associated costs and treatment benefits continue after the observed trial period (see section 3.16)
- using a log-normal extrapolation function to model overall survival (see section 3.17)
- assuming introducing tafamidis would not reduce diagnosis delays and excluding estimated benefits and cost savings associated with earlier diagnosis of ATTR-CM (see sections 3.7 and 3.18)
- including drug wastage in cost estimates (see section 3.19).

These changes resulted in an ICER that was substantially above £30,000 per QALY gained. The committee recalled that it would consider the 2 approaches put forward by the ERG to model treatment stopping in NYHA health states 1, 2 and 3 and that it was not appropriate to model a stopping rule based on the NYHA classification system (see sections 3.13 and 3.14). Using these assumptions in its preferred analysis increased the ICER even more. Considering all these factors, the committee's most plausible ICER for tafamidis compared with best supportive care, in the

full population, was substantially above the range that NICE usually considers an acceptable use of NHS resources (see section 3.23). It concluded that tafamidis was not a cost-effective use of NHS resources for treating ATTR-CM.

Other factors

There are no equalities issues that can be addressed in the guidance

3.25 The committee noted that the most common transthyretin variants associated with hereditary ATTR-CM are Val122Ile which is common in people of African and Caribbean family origin, and Thr60Ala, which is common in people with Irish ancestry. The committee acknowledged that ATTR-CM disproportionately affected people from certain ethnic groups, but agreed this was not something that could be addressed in its recommendations.

The benefits of tafamidis are captured in the economic model

3.26 The company considered that tafamidis is a breakthrough treatment for ATTR-CM. It noted that it is a step-change in managing the condition, and that it will reduce the burden on people with ATTR-CM and their carers. It also highlighted that it was the first treatment for ATTR-CM to reduce mortality and morbidity and reduce cardiovascular-related hospitalisations. It suggested that the high QALY gains seen in the cost-effectiveness analysis represented a major change in managing ATTR-CM. The clinical expert explained that new research had changed their understanding of the way that tafamidis treats ATTR-CM. They suggested that the mechanism by which it works may not be as innovative as was originally thought. The committee acknowledged that there is an unmet need for an effective treatment for ATTR-CM, but considered that the relevant benefits of tafamidis were captured in the economic model.

Conclusion

Tafamidis is not recommended

3.27 The committee recognised that ATTR-CM is a debilitating and progressive condition which has a substantial effect on a person's quality of life (see sections 3.1 and 3.2). It noted that getting a definitive ATTR-CM diagnosis was complicated and it can take a long time for a person to be diagnosed (see section 3.3). Without validated and objective measures for assessing ATTR-CM, identifying people who need treatment and those who are benefiting from treatment will continue to be a challenge (see section 3.5). It acknowledged that tafamidis was more effective than placebo in the outcomes assessed in ATTR-ACT, but it had some concerns about the measure assessed as the primary outcome (see section 3.9). It recalled that there was considerable uncertainty about the modelling of stopping tafamidis and if treatment effects continue after this (see sections 3.14 and 3.15). It also recalled that there was a high degree of uncertainty about whether introducing tafamidis would reduce diagnosis delays and result in any additional benefits or cost savings (see sections 3.7 and 3.18). All this considered, the committee's most plausible range of ICERs was substantially higher than £20,000 per QALY gained, which it considered should apply given the high degree of uncertainty (see section 3.23). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Stephen O'Brien
Chair, appraisal committee
May 2020

5 Appraisal committee members and NICE project team

Appraisal 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 to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The [minutes of each appraisal committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

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

Thomas Paling

Technical lead

Nicola Hay

Technical adviser

Kate Moore

Project manager

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