NICE National Institute for Health and Care Excellence

NICE guidance

Tafamidis for treating transthyretin amyloidosis with cardiomyopathy

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

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. Awareness of ATTR-CM has improved, but accurately diagnosing ATTR-CM can be 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 clinical benefit varies across different types and stages of ATTR-CM. Also, the measure used to assess how severe ATTR-CM is has limitations. This makes it difficult to clearly identify who benefits from tafamidis and whether they should continue treatment.

The cost-effectiveness estimates are higher than what NICE normally considers an acceptable use of NHS resources. This is because there is not enough evidence that recommending tafamidis would reduce diagnosis delays and uncertainty about how long the treatment works after it is stopped. 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)'. Before the marketing authorisation was granted, tafamidis was available in the NHS through the early access to medicines scheme.

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) giving an annual cost of £130,089.88. The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), NICE's 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 There are 2 types 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 transthyretin (TTR) gene.

  The clinical experts explained that ATTR-CM is a progressive disease. Symptoms usually start after age 70 in people with wild-type ATTR-CM or after age 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. Another patient expert explained that ATTR-CM made them feel older than they should and limited them to mostly staying seated. The patient experts 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 across different generations, 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

Awareness of ATTR-CM has improved but diagnosis can still take a long time

3.3 The patient experts explained that getting an accurate diagnosis for ATTR-CM could be challenging. They noted that 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. One patient expert explained that they waited more than 4 years for an accurate diagnosis, highlighting a general lack of understanding about the condition outside of specialist centres. The company highlighted National

Amyloidosis Centre (NAC) data showing that, on average, it took 3 years or more for a person to be accurately diagnosed with ATTR-CM. Two of the clinical experts agreed that there were challenges in diagnosing ATTR-CM accurately, but noted the developments in recent years. Radionuclide imaging (DPD scan), a test usually used to detect bone abnormalities, is increasingly being used to diagnose ATTR-CM. It is very sensitive to detecting amyloid deposits in the heart. This has improved awareness of ATTR-CM and increased diagnoses. Two of the clinical experts highlighted that the low cost of DPD scanning meant most hospitals would be able to do them. So, they expected further increases in ATTR-CM diagnoses. They also noted increased awareness of ATTR-CM after NICE's highly specialised technologies guidance recommended inotersen and patisiran for treating hereditary transthyretin amyloidosis with polyneuropathy (see section 3.5). The committee concluded that the availability of new diagnostic tests and treatments for the disease had improved awareness of ATTR-CM, but recognised that diagnosis can still take a long time.

It is unclear if increased availability of DPD scans will lead to an increase in diagnosing amyloidosis or ATTR-CM

3.4 Two of the clinical experts explained that transthyretin amyloid deposits are often an incidental finding in people having DPD scans and may not necessarily be associated with a diagnosis of ATTR-CM. They explained that the population they see in practice has 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. In addition, because other common comorbidities can lead to increased breathlessness and decreased mobility, reaching a definitive ATTR-CM diagnosis is challenging. At consultation, the company commented that the NAC published a non-invasive diagnostic pathway for ATTR-CM in 2016. It explained that the pathway had been validated and implemented at 17 early access to medicines scheme (EAMS) sites. It further explained that based on this pathway, only people with symptoms and certain clinical features are eligible for DPD scans. So, amyloid deposits identified through the pathway are not incidental. It highlighted that, because of this, amyloid deposits found when doing DPD scans for another condition would not result in a diagnosis of amyloidosis. At the second committee meeting one of the clinical experts confirmed that incidental amyloid deposits would not result in an increase in amyloidosis diagnoses, because other

clinical features outlined in the ATTR-CM diagnostic pathway would be taken into account. The committee questioned whether everybody with heart failure and an abnormal DPD scan would be diagnosed with amyloidosis. One clinical expert explained that not everyone with heart failure would have a DPD scan, and only those with cardiac symptoms specific to ATTR-CM (such as thickening of the heart muscle) would be tested. They further explained that people diagnosed with ATTR-CM and having treatment in clinical practice would likely reflect the population from the ATTR-ACT pivotal trial (see section 3.9) although in the trial a biopsy was required. The clinical experts and the NHS England representative explained that when amyloidosis is suspected people are referred to the NAC for more rigorous testing. The committee was aware that the European public assessment report for tafamidis states that there are difficulties in diagnosing people with ATTR-CM in NHYA class 1, particularly if they do not have heart failure. It also states that an accurate diagnosis cannot be formally established without a number of procedures (such as biopsy and scintigraphy). The committee acknowledged this and agreed that even with DPD scans and a diagnostic pathway, there would still be challenges in diagnosing ATTR-CM. The committee concluded that it was unclear if the increased availability of DPD scans would lead to an increase in diagnosing amyloidosis or ATTR-CM.

Best supportive care is the relevant comparator

3.5 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 (mixed clinical features). 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 transplantation can only take place early in the course of the disease, transplants are rarely done. The committee agreed that transplantation was not an appropriate comparator for tafamidis and concluded that best supportive care was the appropriate comparator.

Measuring ATTR-CM severity using NYHA classification has limitations but there is insufficient trial evidence to consider an alternative

3.6 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. But 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. One clinical expert noted that variability in how people classify themselves was a common issue with all symptom-based measures. They also highlighted that the NYHA classification system is used as an entry criterion in most heart failure trials. The clinical experts commented that it was 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 ERG explained that there were merits to assessing disease severity using objective measures such as cardiac markers. But it commented that in the ATTR-ACT pivotal trial (see section 3.9), unlike the NYHA classification which was measured every 6 months, these cardiac markers were only measured at baseline, month 12, and after stopping treatment. So, they were not measured frequently enough to accurately characterise the disease. The committee concluded that using the NYHA classification in ATTR-CM had limitations, but acknowledged that there was insufficient trial evidence available to consider an alternative. This was because cardiac markers, which could have been used to identify disease stage and who would benefit from treatment, were not measured frequently enough in the trial.

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

3.7 The marketing authorisation for tafamidis does not specify starting and stopping rules for tafamidis based on the NYHA classification system. The company highlighted that NYHA classifications have been incorporated in previous NICE recommendations to define populations eligible for treatment with heart failure therapies. The committee 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 committee recalled that NYHA class 1 means that people can do ordinary physical activity (see section 3.6). 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. At consultation, the company highlighted that this contradicted tafamidis' marketing authorisation, which states that treatment should be started as soon as possible. The company

proposed a stopping rule in which people would stop tafamidis if their disease progressed to NYHA class 4. It explained that there was limited evidence to support using tafamidis in people whose disease was NYHA class 4, who had severe heart failure symptoms, because they were excluded from the ATTR-ACT pivotal trial. Also, the company highlighted that its proposed stopping rule reflected treatment stopping in ATTR-ACT, in which most people stopped tafamidis quickly after progressing to NYHA class 4. It also noted that because tafamidis does not improve symptoms caused by ATTR-CM it would be clinically appropriate to stop treatment when a person's disease is classed as NYHA 4. A clinical expert noted that stopping treatments when the disease progresses to NYHA class 4 was common because at this stage people are very unwell. They explained that people would be unable to travel for treatment, so treatment would likely be stopped and best supportive care offered. Comments from the patient organisation supported this view, stating that making decisions about stopping treatment in advanced disease stages were not uncommon. Conversely, 2 of the clinical experts noted that it would be challenging to stop treatment when disease progressed to NYHA class 4 because no alternative treatments were available. These 2 clinical experts also explained that people's disease often varies between NYHA class 3 and 4 and that this was typical of ATTR-CM. They noted that some people whose disease was classed as NYHA 4 could improve, so could change to NYHA class 3 or better. The ERG noted that improvements shown by changes in NYHA class were also seen in ATTR-ACT. The committee recalled that the company's proposed stopping rule was not specified in tafamidis' marketing authorisation. It agreed, that on balance, it would be difficult for clinicians to implement a stopping rule for tafamidis. This was because the disease can often vary between NYHA class 3 and 4 and the lack of alternative treatments for NYHA class 4 disease meant people would likely prefer to keep taking tafamidis. The committee concluded that using the NYHA classification alone to accurately define the population who were eligible to have tafamidis had limitations. So, it also concluded that it would not consider starting and stopping rules for tafamidis based on the NYHA classification system in its decision making.

There is not enough evidence that tafamidis would reduce delays in diagnosis times

3.8 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. The company also noted that since tafamidis became available in the EAMS, the proportion of people whose disease was diagnosed in NYHA class 1 or 2 has increased from 75% to 86%. The committee understood that the short-term observational EAMS data were presented to support the assumption that introducing tafamidis could reduce diagnosis delays. It acknowledged that although the EAMS data were informative, they can only show that diagnosis delays were reducing when tafamidis was available. They cannot show that the delays were reducing because of tafamidis. A statement from NHS England suggested that if NICE recommended tafamidis, and awareness was increased through educational campaigns, diagnosis rates may improve further. The committee recalled that average time to diagnosis at the NAC was 3 years or more (see section 3.3). The company noted that 1 in 3 patients were diagnosed in less than 6 months, while 40% waited for 4 years or more. The committee acknowledged that reducing the average time to diagnosis to less than 6 months would represent a substantial improvement. But, it recognised these diagnoses were made at a specialist centre and questioned if such reductions could be achieved at other centres in clinical practice. The ERG highlighted that the trend of earlier diagnosis seen in the EAMS could be explained by improvements in diagnostic tools since the ATTR-ACT pivotal trial (see section 3.3). It noted that when ATTR-CM is suspected the diagnostic pathway may lead to quicker diagnoses, but when it is not suspected, substantial diagnosis delays may still occur. The committee acknowledged this, and agreed it was not possible to attribute reductions in diagnosis times at EAMS sites to the availability of tafamidis. It also noted web comments at consultation which highlighted evidence of an increasing number of ATTR-CM diagnoses at the NAC before tafamidis was available through EAMS. There were also comments from the EAMS centres' cardiac group that a major contributor to the shorter diagnosis times was the changes in diagnostic tools and algorithms. The committee also recalled that awareness of ATTR-CM had increased (see section 3.3) and questioned whether recommending tafamidis would further increase awareness and reduce diagnosis times. The committee concluded that there was not enough evidence provided to support the assumption that introducing tafamidis would reduce ATTR-CM diagnosis delays.

Clinical evidence

The ATTR-ACT trials are appropriate for decision making

3.9 The clinical evidence came 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, 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 pivotal trial 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 states 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 trials were appropriate for decision making.

Tafamidis is more effective than placebo in clinical trial results

3.10 The primary analysis from the ATTR-ACT pivotal trial 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 all-cause mortality and cardiovascular-related hospitalisations, was assessed in a hierarchical analysis using the Finkelstein-Schoenfeld method. At month 30, 186 people (70.5%) were alive in the tafamidis group compared with 101 people (57.1%) in the placebo group. 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). Tafamidis statistically significantly reduced all-cause mortality and frequency of cardiovascular-related hospitalisations compared with placebo. The committee considered that although the parts of the primary outcome were clinically relevant to patients and clinicians, it questioned

whether the combined measure would be considered 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 results are not suitable for decision making

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

- hereditary and wild-type ATTR-CM (see section 3.1) and

- either NYHA class 1 or 2 or NYHA class 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 all-cause 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 reduced 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. Two of 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, recognising that ATTR-ACT was powered on the primary outcome measure (see section 3.10). 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. One of the clinical experts highlighted that cardiovascular-related mortality reduced for people whose disease was classed as NYHA 3. Although the reduction was not as large as in those whose disease was classed as NYHA 1 or 2, it was encouraging for a subgroup of people with a poor prognosis. The committee agreed that although the subgroup results added a degree of uncertainty around tafamidis' clinical effectiveness it accepted they were underpowered. So, it concluded they would not be considered in its decision making.

Quality of life

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

3.12 Quality of life was measured in the ATTR-ACT pivotal trial 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

3.13 Most of the adverse events of treatment seen in the ATTR-ACT pivotal trial 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

3.14 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 3.6). The model included 5 health states, 4 defined by NYHA classes (1, 2, 3, and 4) and 5 being death. People could 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 3.6), 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

3.15 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 class 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 3.6, 3.7 and 3.11). The committee recalled that the NYHA classification is widely used to define populations eligible for heart failure treatments and has been used in previous NICE recommendations (see section 3.7). But, it noted that although the tafamidis marketing authorisation states that there were limited clinical data in patients whose disease was classed as NYHA 4, it did not specify that it should be stopped (see section 3.7). The committee also recalled that it would be difficult for clinicians to implement a stopping rule for tafamidis. This was because the disease can often vary between NYHA class 3 and 4 and the lack of alternative treatments for NYHA class 4 disease meant people would likely prefer to keep taking tafamidis (see section 3.7). The committee was aware that when considering treatment continuation rules, it needed to take additional factors into account as well as the cost-effectiveness estimates based on continuing treatment only in those whose disease had a specified response (see NICE's guide to the methods of technology appraisal). These factors include:

- the robustness and plausibility of the endpoint on which the rule is based
- whether the rule can be incorporated into routine clinical practice
- considerations of fairness with regard to withdrawal of treatment from people whose condition does not respond to treatment.

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 of the limitations of using the NYHA classification system in ATTR-CM. Also, a stopping rule was not specified in the marketing authorisation and stopping treatment based on NYHA classification could be challenging to do in clinical practice.

It is unrealistic to assume continued treatment benefits without a cost

3.16 After technical engagement, the company included a treatment stopping rule for people in the NYHA class 1 to 3 health states. During technical engagement, a clinical expert explained that it was unlikely people would stop tafamidis in NYHA class 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 class 1 to 3 health states in its revised analysis. The ERG explained that in the economic model, people in the NYHA class 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. A clinical expert at the second committee meeting also noted that no evidence was available to support such an assumption. The company noted that the relative treatment effect for tafamidis was estimated from the ATTR-ACT pivotal trial and incorporated the treatment effects for people who remained on treatment and those who stopped. So the effect of stopping treatment is already accounted for in its treatment effectiveness estimates. It also suggested that it is clinically plausible for benefits to continue after treatment stops because tafamidis' mechanism of action reduces cumulative

amyloid exposure. So, the longer a person is on treatment, the more their cumulative exposure is reduced. Research group comments received at consultation suggested that ATTR-ACT had not revealed anything about how tafamidis works. The group stated that a recent publication had shown that disease stabilisation does not necessarily inhibit amyloid formation, so the mechanism underlying tafamidis' proposed benefit is unclear. The ERG reiterated that the limitations of the company's approach were acknowledged at technical engagement. It highlighted that the company failed to make use of longer-term data in its extrapolation of treatment stopping. 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

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

- The first analysis continued to model treatment stopping in NYHA class 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 class 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 class 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 3.15), 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 everyone in the NYHA class 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 (see section 3.16). 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. The company commented that, unlike its approach of extrapolating the observed trial data, the ERG's analyses introduced unnecessary assumptions. 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

3.18 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). At consultation the company changed the extrapolation to reflect a new ATTR-ACT extension study data cut,

which suggested that survival benefits increased the longer people were on tafamidis. It explained that because the estimated survival benefits from the ATTR-ACT extension study included people who had swapped from placebo to tafamidis, mortality benefits were likely to be underestimated. So, because of this, and because the 2 extrapolation functions were similar in statistical and visual fit, it suggested it was appropriate to use the more optimistic of the two. The ERG noted that according to the Bayesian information criterion the generalised gamma extrapolation function used by the company was the worst fit. The committee concluded that modelling overall survival using generalised gamma extrapolation functions was not fully justified. It 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

3.19 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 2.50 years to 71.95 years
- avoided £20,000 of healthcare costs that would be incurred during the time people waited for a correct diagnosis

- avoided anxiety and depression because of diagnosis delays.

The committee recalled that there was not enough evidence provided to support the assumption that introducing tafamidis would reduce ATTR-CM diagnosis delays (see section 3.8). 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. The company explained that 1 in 3 people in the EAMS had an accurate diagnosis 2.5 years earlier (within 6 months) than the historical average (3 years or more; see section 3.3). It noted that if other centres had access to the same tests used in the EAMS, diagnosis times of 6 months or less could be replicated for all patients. The committee agreed it was unlikely that delays could be reduced by 2.5 years for all patients and that it was difficult to predict how the diagnosis times might change in the future. It was also aware that reducing the average age of starting treatment by 2.5 years had a modest effect on the cost-effectiveness results compared with the other early diagnosis assumptions. Also, if only a proportion of patients had a shorter time to diagnosis, then the effect on cost effectiveness would be small. The company also explained that the cost-saving estimate of £20,000 resulting from earlier diagnosis was calculated based on NAC data, which reported resource use during a 3-year diagnosis delay. It acknowledged that empirical estimates for reduced hospital, primary care and imaging resource use could not be provided. But, it noted that the cost-saving assumption showed that earlier diagnosis of ATTR-CM could affect cost-effectiveness estimates. The committee acknowledged that some of the costs incurred during diagnosis delays could be avoided. But, it agreed that because there was insufficient evidence to support the assumption that introducing tafamidis would reduce ATTR-CM diagnosis delays, it was highly uncertain if any costs could be avoided. The company 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 everyone would have depression, but the analysis showed the potential effect of earlier diagnosis on people's quality of life. The ERG 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. The committee agreed that there was insufficient evidence to support the assumption that introducing tafamidis would reduce ATTR-CM diagnosis delays (see section 3.8). It also agreed that

it was highly uncertain whether any additional cost savings or quality-of-life benefits resulting from earlier diagnosis could be attributed to tafamidis. So, it concluded that the company's early diagnosis assumptions in the model were not appropriate for decision making because there was not enough evidence to support them.

Including drug wastage costs is appropriate

3.20 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 including drug wastage in the 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

3.21 The company derived health state utility values using EQ-5D-3L data from the ATTR-ACT pivotal trial. The committee recalled that the company had also collected quality-of-life data using the KCCQ measure, which included function domains (see section 3 12). 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, but agreed that they could be considered because there was no available alternative (see section 3.14). 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

3.22 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. The committee concluded that using age-adjusted utility values was appropriate.

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

3.23 The company estimated health state utility values separately for each NYHA class (see section 3.21) and treatment included in the model. It 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 3.6). The ERG noted that the company modelled substantially different on- and off-treatment utility values in the NYHA class 4 health state. It also explained that estimates of NYHA class 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 the ATTR-ACT pivotal trial 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 class 4. The ERG explained that the estimated NYHA class 4 utility value for tafamidis could be affected by informative censoring, because the quality of life of anyone who stopped tafamidis in NYHA class 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 class 4 health state. After technical engagement the company accepted that it was appropriate to apply the best supportive care utility value in NYHA class 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 class 1 to 3, and that the best supportive care utility value should be applied in the NYHA class 4 health state.

Cost-effectiveness estimates

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). It included the following assumptions:

- a stopping treatment rule for tafamidis in NYHA health states 1, 2 and 3 (see section 3.16)
- using a generalised gamma extrapolation function to model overall survival (see section 3.18)
- a stopping treatment rule for tafamidis if disease progressed to NYHA class 4 (see section 3.15)
- an earlier treatment starting age and estimated cost savings and benefits associated with earlier diagnosis of ATTR-CM (see sections 3.8 and 3.19)
- health state utility values adjusted for age (see section 3.22)
- treatment-independent health state utility values in NYHA 4 equal to best supportive care values (see section 3.23).

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 3.18)
- assuming introducing tafamidis would not reduce diagnosis delays and excluding estimated benefits and cost savings associated with earlier diagnosis of ATTR-CM (see sections 3.8 and 3.19)

- including drug wastage in cost estimates (see section 3.20).

These changes resulted in an ICER that was substantially above £30,000 per QALY gained. The committee recalled that it would consider the ERG's 2 approaches 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 3.15 and 3.17). 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. 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 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 disproportionally affected people from certain ethnic groups, but agreed this was not something that could be addressed in its recommendation. A statement received at consultation noted that the recommendation would deny older people with ATTR-CM access to tafamidis, which could maintain their health and reduce morbidity, while those in the EAMS could have tafamidis. The committee was also aware that evidence suggested ATTR-CM prevalence in women may be underestimated, because women may be less likely to have the red flag symptoms that trigger referral. The committee considered that its recommendation did not disproportionately disadvantage women or certain age groups, and that access to tafamidis through the EAMS was not in the scope of their recommendation.

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 benefit 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. The committee recalled that a recent publication had shown that disease stabilisation does not necessarily inhibit amyloid formation, so the mechanism underlying tafamidis' proposed benefit is unclear (see section 3.16). 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 awareness of ATTR-CM was improving but getting a definitive diagnosis was complicated and can take a long time (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 3.6). It acknowledged that tafamidis was more effective than placebo in the outcomes assessed in the ATTR-ACT pivotal trial. It recalled that there was considerable uncertainty about the modelling of stopping tafamidis and if treatment effects continue after this (see sections 3.15 and 3.16). 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 that could be attributed to tafamidis (see sections 3.8 and 3.19). All this considered, the committee's most plausible range of ICERs was substantially above the range that NICE usually considers an acceptable use of NHS resources (see section 3.24). So, the committee did not recommend using tafamidis in the NHS for treating ATTR-CM.

4 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.

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Accreditation